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REVIEW

# Cell-based regenerative interventions in Parkinson's disease: Overcoming pharmacological limitations

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**Abstract** Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic (DA) neurons and the pathological aggregation of α-synuclein. While current pharmacological therapies provide symptomatic relief, they do not halt or reverse disease progression. Cell-based regenerative strategies have emerged as promising approaches to restore DA function and target the complex, multifactorial pathophysiology of PD. This review critically examines current approaches, including transplantation of fetal ventral mesencephalic tissue, pluripotent stem cell-derived midbrain DA progenitors, and *in vivo* reprogramming of endogenous cells. In addition, supportive cell types, such as mesenchymal stromal cells and carotid body glomus cells, provide neuroprotective and immunomodulatory effects *via* paracrine signaling. We summarize preclinical and clinical evidence on graft survival, integration, and functional recovery, and discuss key determinants of therapeutic efficacy, including mitochondrial function and bioenergetic integrity, immune compatibility, and biomaterial scaffolding. Despite significant progress, major challenges remain regarding long-term efficacy, graft standardization, and host −graft interactions. Ongoing translational advances are poised to drive the development of disease-modifying cell therapies capable of delivering durable clinical benefits and improving long-term outcomes in PD.



## 1. Introduction

Parkinson's disease (PD) is a chronic, age-associated neurodegenerative disorder characterized by the progressive loss of A9 dopamine (DA)-producing neurons in the substantia nigra (SN)[1]. Neurodegeneration typically initiates distally, with retraction of axon terminals and concomitant reduction in DA content within the caudate-putamen (striatum) (Fig. 1A). This process is accompanied by pathological aggregation of α-synuclein (α-SYN) into Lewy bodies (LBs) and Lewy neurites (Fig. 1B, original illustration generated by the authors for this manuscript)[2,3]. These inclusions, often co-localized with ubiquitin and p62, disrupt neuronal homeostasis and accelerate neurodegeneration. Under physiological conditions, α-SYN regulates synaptic vesicle trafficking, neurotransmission, and mitochondrial ATP synthesis[4-6]. In contrast, α-SYN pathological aggregation, influenced by post-translational modifications[7,8], spreads from limbic regions toward the neocortex[9], thereby disturbing synaptic organization and proteostatic balance[3,10-12]. Nuclear inclusions known as Marinesco bodies, detected within DA neurons, are associated with reduced striatal DA markers and may further exacerbate to neuronal vulnerability (Fig. 1B)[13].

Loss of striatal DA underlies the core motor symptoms of PD, including resting tremor, bradykinesia, rigidity, and postural instability (Fig. 2A)[14,15], which arise from impaired basal ganglia circuits and higher-order cognitive processes[16,17]. In addition, patients exhibit a broad range of non-motor symptoms (Fig. 2B), including cognitive decline, mood disorders, sleep disturbances, autonomic and gastrointestinal dysfunction, and sensory deficits, all of which substantially reduce quality of life[18-21]. DA metabolism is tightly controlled by tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase, vesicular monoamine transporter 2 (VMAT2), and the DA transporter (DAT) (Fig. 3)[22]. Early dysfunction of VMAT2 or DAT may occur before overt neuronal loss[23], while oxidative metabolism of DA generates reactive oxygen species (ROS) and toxic aldehydes, promoting mitochondrial dysfunction and apoptosis[24]. Converging mechanisms, including neuroinflammation, glial activation, and impaired proteostasis further increase neuronal vulnerability, reflecting the multifactorial nature of PD pathogenesis[25-28].

Despite significant advances in pharmacological and surgical management, current therapeutic approaches, such as levodopa (L-DOPA), deep brain stimulation (DBS), and transcranial static magnetic stimulation (tSMS), remain largely symptomatic and do not alter the underlying neurodegenerative process. Although L-DOPA therapy is initially effective, chronic administration often leads to motor fluctuations and dyskinesias in up to half of patients within five years, offering limited benefit for cognitive and autonomic symptoms[29-32]. DBS can alleviate selected motor deficits, but it is invasive, expensive, and fails to modify the underlying disease progression[33,34]. tSMS is a non-invasive neuromodulatory technique that transiently modulates motor cortex excitability[35]. In a randomized, sham-controlled trial in PD, repeated tSMS was safe but showed no significant objective reduction in L-DOPA-induced dyskinesias, despite moderate subjective improvement, reflecting its short-lived effects and the need for longer, controlled studies[36]. Therefore, there is an urgent need for therapies that restore lost DA function and alter disease trajectory. In this context, cell-based regenerative therapies have emerged as one of the most promising disease-modifying approaches for PD[37]. Preclinical studies in rodent and non-human primate models have demonstrated that transplanted DA progenitors can survive long-term, extend axons to appropriate striatal targets, and restore motor function[38-44].

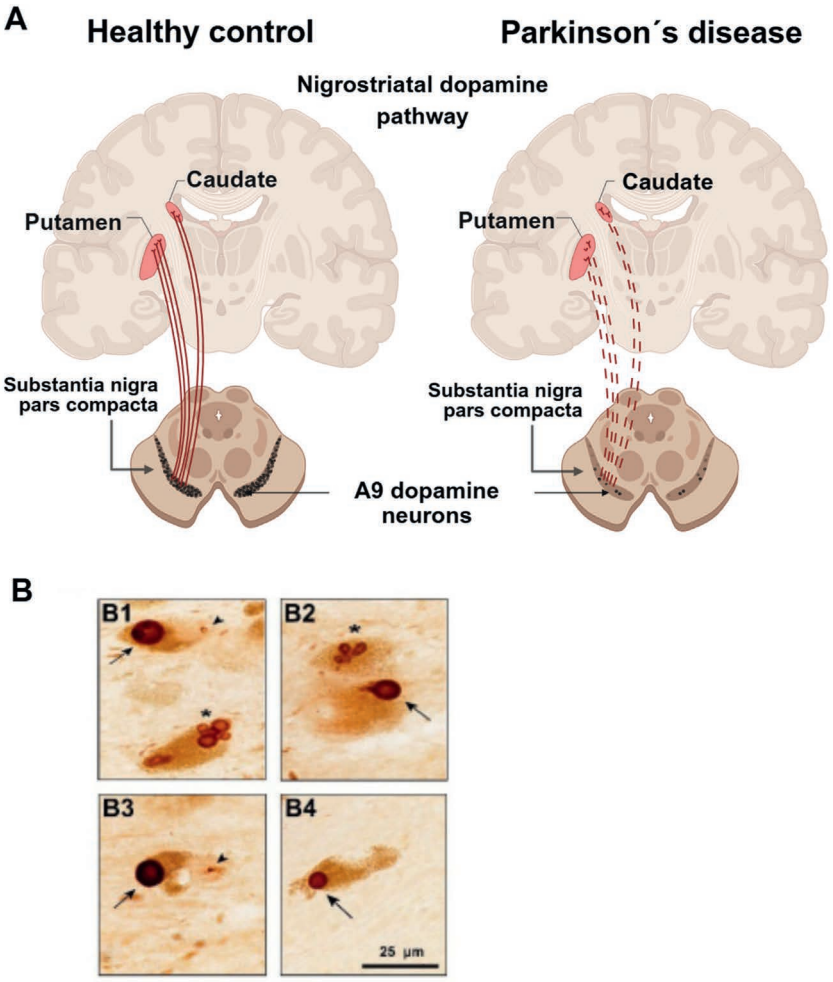


**Figure 1** Nigrostriatal dopaminergic degeneration and the formation of Lewy bodies and Marinesco bodies as core neuropathological hallmarks of Parkinson's disease. (A) Selective degeneration of A9 dopamine (DA) neurons in the substantia nigra (SN) pars compacta and loss of their striatal nerve terminals. (B) Post-mortem Parkinson's disease (PD) midbrain sections showing Lewy body (LB) pathology in pigmented SN neurons. LBs (arrows) appear as ring-shaped inclusions with an immunoreactive peripheral halo and a paler core. Multivesicular LBs, characterized by multiple inclusions within a single DA neuron, are indicated by stars. Small nuclear inclusions known as Marinesco bodies (arrowheads), considered markers of advanced aging and PD, are also visible. Scale bar = 25 µm. Illustration created by the authors for this article.

Early clinical trials using fetal ventral mesencephalic (fMV) tissue confirmed the feasibility of DA replacement in patients[45-48]. More recently, first-in-human trials employing human induced pluripotent stem cell (hiPSC)-derived midbrain DA progenitors have demonstrated graft survival, local DA production, favorable safety profiles, and preliminary functional improvements at short-to mid-term follow-up[49-51], marking a pivotal advance toward clinical translation. Parallel clinical investigations using mesenchymal stromal cells (MSCs) and carotid body (CB) glomus cells have demonstrated favorable safety and tolerability, with some patients showing modest yet measurable improvements in motor function, daily activities, and medication requirements, partially sustained for up to three years[52-55]. Collectively, these results support the feasibility of autologous grafting strategies and justify further controlled studies to determine long-term efficacy in PD.

Recent advances in regenerative medicine now extend beyond simple neuronal replacement toward combinatorial strategies that integrate immune engineering, bioengineering, and metabolic resilience. Ongoing efforts include the generation of hypoimmunogenic iPSC lines, human leukocyte antigen (HLA)-edited donor cells, and regional haplobanks to mitigate immune rejection[56,57], as well as interventions to prevent host-to-graft $\alpha$-SYN propagation through the synuclein alpha gene (*SNCA*)-edited cells and $\alpha$-SYN-targeted immunotherapies[58-62]. Innovations in biomaterials, such as biomimetic hydrogels, engineered scaffolds, and localized delivery systems, are further enhancing graft survival, axonal integration, and host tissue repair[42,63-66]. In parallel, emerging strategies including astrocyte-to-neuron reprogramming[67,68], extracellular vesicle-mediated neurorepair[69,70], and approaches aimed at preserving mitochondrial function and bioenergetic resilience[71,72], are expanding the therapeutic scope of regenerative interventions. Collectively, these developments mark a transition from proof-of-concept studies to multimodal, clinically scalable regenerative platforms that integrate optimized donor cells with immune, mitochondrial, and bioengineering innovations to achieve durable, disease-modifying benefits in PD.

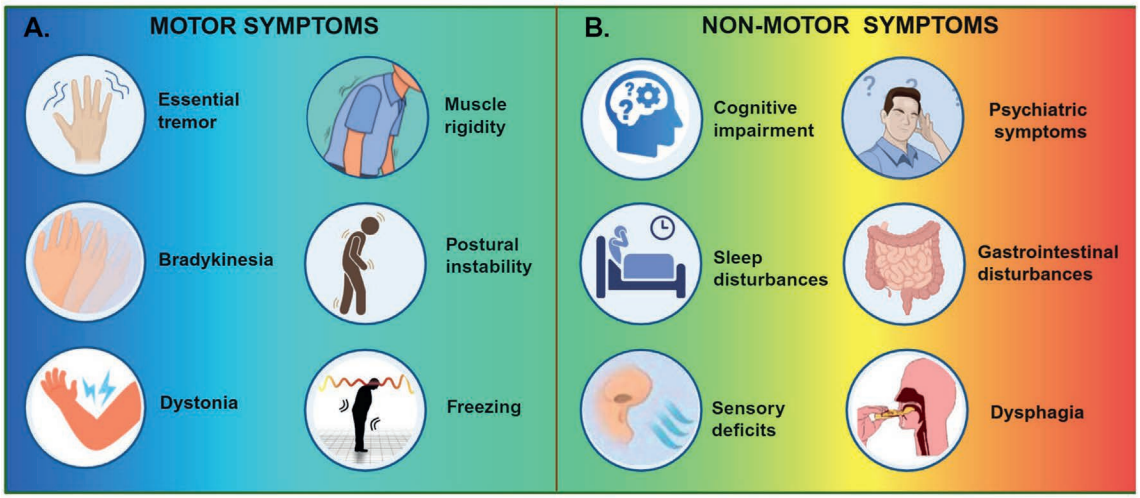


**Figure 2** Common clinical signs of Parkinson's disease. (A) Motor symptoms encompass essential tremor, bradykinesia, dystonia, muscle rigidity, postural instability, and episodes of freezing of gait. These features reflect progressive loss of dopaminergic control over voluntary movement. (B) Non-motor symptoms include cognitive impairment, sleep disturbances, sensory abnormalities, mood disorders, and autonomic dysfunction, which often emerge early and substantially contribute to patient disability and reduced quality of life.

This review provides a comprehensive overview of the mechanistic rationale, therapeutic progress, and translational challenges of cell-based interventions for PD, emphasizing their potential to improve both motor and non-motor outcomes. It further emphasizes emerging combinatorial strategies and the integration of regenerative medicine with precision

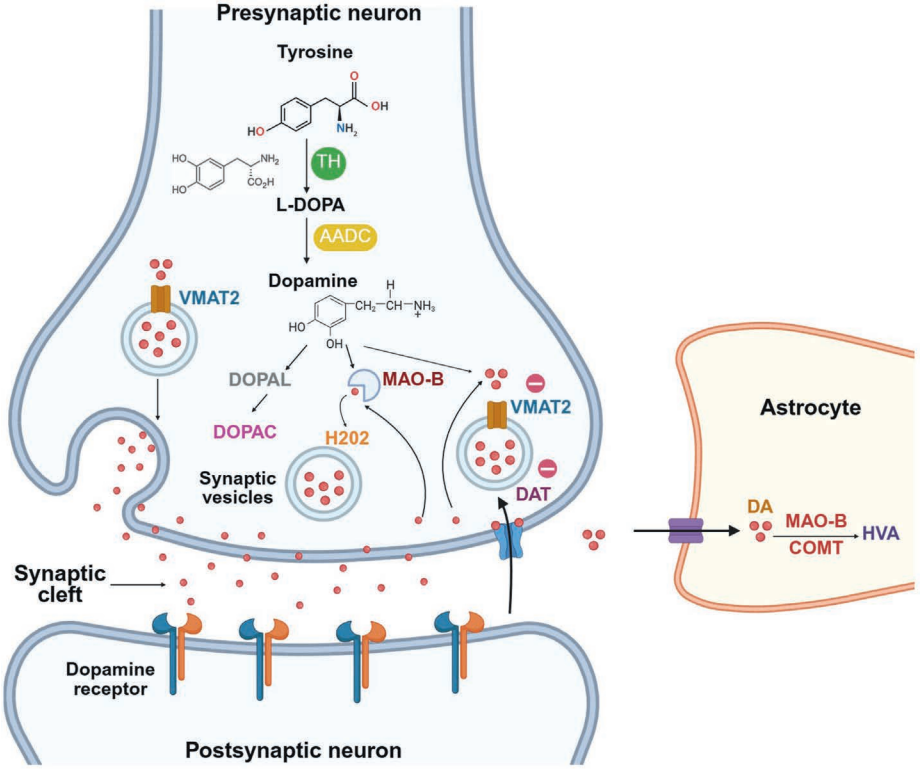


**Figure 3** Dopamine synthesis, release, reuptake, and metabolism. Tyrosine is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase (TH), and L-DOPA is then converted to dopamine (DA) by aromatic L-amino acid decarboxylase (AADC) in the presynaptic neuron. DA is loaded into synaptic vesicles by vesicular monoamine transporter 2 (VMAT2) and released into the synaptic cleft, where it binds to dopamine receptors on the postsynaptic neuron. Unbound DA is either returned to the presynaptic neuron through the dopamine transporter (DAT) or broken down by monoamine oxidase B (MAO-B) to 3,4-dihydroxyphenylacetaldehyde (DOPAL) and then 3,4-dihydroxyphenylacetic acid (DOPAC), producing hydrogen peroxide ($H_2O_2$). Astrocytes also clear DA, where MAO-B and catechol-*O*-methyltransferase (COMT) convert it to homovanillic acid (HVA).

bioengineering as a roadmap for next-generation disease-modifying therapies.

## 2. Axonal degeneration as an early pathological hallmark of Parkinson's disease

Axonal pathology precedes neuronal death, involving early degeneration that disrupts neuronal connectivity before the loss of the perikarya. This process is marked by progressive cytoskeletal disintegration, transport deficits, and synaptic dysfunction, ultimately causing axonal retraction and fragmentation, and contributing to the onset of both motor and non-motor symptoms in PD. The temporal progression of axon degeneration has been characterized in transected axon models[73], revealing three phases: an acute degeneration phase affecting both proximal and distal segments immediately post-injury[74,75], a latency period during which distal axons maintain structure and transient excitability[76,77], and a rapid granular degeneration phase marked by swift cytoskeletal disintegration distal to the lesion[78,79].

DA neurons exhibit a remarkably extensive and intricately structured axonal network, defined by a tightly packed and widely distributed branching pattern, enabling broad neuromodulatory regulation across multiple target regions. Morphological analyses in rats report total axonal lengths ranging from $1.4 \times 10^5$ to $7.8 \times 10^5$ μm for a single DA neuron in the dorsal tier of the SN, and $5 \times 10^5$ to $6.1 \times 10^5$ μm in the ventral tier [80]. A single DA neuron in the rat SN forms approximately 100,000 to 250,000 synaptic connections, reflecting its highly branched architecture and extensive influence within the striatum[81]. These variations underscore the complex and region-specific arborization of DA neurons essential for their distinct functional roles in cognitive processing and motor control within basal ganglia circuitry.

Structural studies also show that the axon initial segment (the critical site for action potential initiation) in DA neurons of the mouse SN averages 25.8 μm in length, with an average of one synapse per neuron[82]. Due to challenges in direct human measurements, estimates of DA neuron axonal architecture derive from extrapolations of animal models and human anatomical data. Assuming conservation of fundamental organizational principles, a single SN DA neuron in humans is estimated to extend an axon approximately 4.5 m long and form between 1 and 2.4 million synapses[81].

Distinct DA neuron populations display significant variations in intrinsic biophysical properties and input-output dynamics, reflecting functional heterogeneity within the nigrostriatal system[83,84]. However, all DA neuron subtypes share exceptionally high metabolic demands due to their extensive axonal arborization. To meet these demands, DA neurons are densely enriched with mitochondria and exhibit elevated oxidative phosphorylation, ensuring efficient ATP synthesis to support their complex activities[85].

Axonal pathology typically originates at the distal end (axon terminal) and advances proximally in a "dying-back" pattern. Morphological alterations begin with swelling and microtubule disassembly, progressing to cytoskeletal fragmentation. DA subpopulations exhibit varying vulnerability to neurodegeneration. In PD, neurons within the ventrolateral SN are most susceptible[86,87]. This susceptibility likely reflects intrinsic and/or acquired susceptibility to α-SYN aggregation[88]. The loss of DA nerve terminals in the dorsal striatum exceeds the death of DA neurons in the SN and is characterized by disrupted structural integrity, concomitant alterations in DA metabolism, and dysregulated neurotransmitter release[89].

Striatal DAT binding is a key indicator of DA terminal density and innervation integrity. DAT imaging with [$^{123}$I]FP-CIT single-photon emission computed tomography is a well-established tool for differential diagnosis of PD and other neurodegenerative parkinsonism versus non-neurodegenerative tremor disorders[90-92]. The positron emission tomography (PET) radiotracer $^{18}$F-DOPA, a fluorinated form of L-DOPA, assesses presynaptic DA integrity and function in clinical and research settings[93-95]. Fluorodopa ($^{18}$F-DOPA) uptake is also valuable for examining graft survival and function following neuronal transplantation[45,96,97]. Synaptic density can be measured using PET with the radioligand [$^{11}$C]UCB-J, which binds to the synaptic vesicle glycoprotein 2A[98]. Advances in magnetic resonance imaging have further enhanced analysis of DA functional activity and denervation[99-101].

Postmortem studies provide definitive evidence of progressive DA terminal degeneration coinciding with disease onset. DAT antibodies selectively detect DA projections in the striatum, while TH antibodies identify DA neurons, although expression of both markers varies with disease progression and regulatory mechanisms. Immunohistochemical analysis reveals a significant reduction (35%−75%) in TH and DAT signals in the dorsal putamen of PD subjects within 1−3 years post-diagnosis, worsening to 70%−90% by 5 years, followed by relative stabilization[87].

Unbiased stereological quantification has revealed a substantial, yet variable, reduction (50%−90%) in TH-positive neurons in patients with PD compared to controls, a loss that is already apparent in the early stages of the disease. Subjects with shorter disease duration exhibit similar TH cell loss to those diagnosed over 20 years earlier, with only minimal additional loss (<20%) thereafter, leaving a residual neuronal population detectable decades post-diagnosis[87]. Quantitative analyses also demonstrate significant downregulation of TH and DAT at protein and mRNA levels in PD brain tissue relative to age-matched controls[102-105].

Collectively, these findings highlight axonal degeneration as a critical early event in PD, preceding neuronal death and driving synaptic dysfunction. The highly branched and metabolically demanding architecture of SN DA neurons renders them particularly vulnerable to degenerative stressors. Postmortem analyses and advanced imaging consistently demonstrate marked reductions in DA markers, underscoring the central role of axonal pathology in disease progression. The variability in neuronal susceptibility suggests both intrinsic factors (such as axonal architecture and metabolic burden) and extrinsic contributors (including α-SYN aggregation and neuroinflammation). Since axonal dysfunction precedes perikaryal loss, targeting axonal maintenance and synaptic integrity offers promising avenues for neuroprotection.

Importantly, this axon-first model reframes regenerative therapies, including cell-based interventions. Traditional strategies focus primarily on restoring lost neuronal somata within the SN, yet their success depends fundamentally on grafted DA neurons' ability to develop extensive, functional axonal projections capable of reinnervating widespread targets, especially the dorsal striatum. The immense anatomical complexity and bioenergetic demands of human nigrostriatal DA neurons (requiring reconstruction of millions of synapses over meter-long axons) pose formidable challenges to regeneration.

Therefore, integrating knowledge of axonal degeneration dynamics and selective vulnerability into cell therapy design is

essential. Future efforts must prioritize not only survival and phenotypic fidelity of grafted cells but also their capacity for axonal growth, target-specific synaptogenesis, and long-term integration into host circuits. Combining regenerative approaches with molecular strategies that enhance axonal resilience and outgrowth may significantly improve therapeutic outcomes in PD[106]. The following section examines cell-based therapies developed to address these anatomical and physiological demands, highlighting how advances in transplantation biology aim to meet the unique structural and metabolic challenges of the nigrostriatal system.

## 3. Neuroregenerative cell-based therapies for Parkinson's disease

Most current pharmacological and surgical interventions for PD primarily target motor symptoms but do not modify the underlying disease course. Their effectiveness declines over time as degeneration of the nigrostriatal system advances and the capacity for DA storage and release diminishes. L-DOPA, the cornerstone of PD therapy, provides robust symptomatic relief but is associated with long-term complications, including motor fluctuations, dyskinesias, and non-motor adverse effects such as hallucinations, fatigue, and cognitive impairment[32]. Disease severity and progression are commonly assessed using the Hoehn and Yahr (HY) scale and the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which together evaluate motor and non-motor deficits throughout the disease course[107-109]. L-DOPA-induced dyskinesias result from complex alterations in neurotransmitter systems, including glutamate, serotonin, and GABA, combined with dysregulated intracellular signaling and gene expression[110]. These limitations emphasize the critical need for interventions that restore DA circuitry and neuronal function rather than simply relieving symptoms.

Cell-based regenerative therapies have arisen as a promising strategy to address this unmet clinical need. These approaches aim to replace lost DA neurons, restore striatal innervation, improve motor and non-motor functions, and modulate immune and inflammatory responses. Advances in stem cell biology and cellular reprogramming have expanded the repertoire of transplantable DA neurons, enabling the potential for patient-specific regenerative interventions [111]. Multiple cell types are under investigation, including fetal midbrain (fVM) tissue, iPSCs, MSCs, and CB glomus cells. Each cell source exhibits distinct neurorestorative potential, immunogenic profiles, and translational scalability (Fig. 4). The following subsections describe these strategies and the rationale for their selection in PD therapy.

### *3.1. Embryonic ventral mesencephalic tissue grafts*

fVM tissue has long been explored as a therapeutic approach in PD due to its high content of A9 DA neurons, the subtype most affected in PD. These neurons can endogenously synthesize and release DA, extend axons over long distances, and integrate into host circuitry to support motor recovery. The fVM includes DA neurons from the retrorubral field (A8), SN pars compacta (A9), and ventral tegmental area (A10), each contributing distinct physiological roles and projection patterns[112].

Successful transplantation depends on graft survival, axonal outgrowth, host integration, and restoration of DA-mediated neurotransmission. Preclinical studies in 6-hydroxydopamine (6-OHDA)-lesioned rodents[113-117] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-injected non-human primates[118-120] demonstrated that fVM grafts can survive, reinnervate the host brain, and restore motor function. In humans, unilateral fVM transplantation into the putamen resulted in increased DA synthesis and improvements in rigidity, bradykinesia, and motor fluctuations[97,121-123]. Table 1[46-48,97,113-128] provides an overview of the key preclinical and clinical findings discussed above.

Follow-up periods ranging from 12 to 46 months have reported improvements in quality of life, increased striatal $^{18}$F-DOPA uptake, and robust graft survival. A double-blind, sham-controlled trial demonstrated graft survival in 85% of patients and significant motor improvements, particularly in younger individuals[124]. In contrast, bilateral ectopic nigral transplants failed to improve MDS-UPDRS scores and were associated with postoperative dyskinesias[125].

Postmortem analyses have confirmed long-standing graft viability. In two patients, striatal transplantation of embryonic DA cell suspensions restored $^{18}$F-DOPA uptake, reduced dyskinesias, and enabled extensive reinnervation[47]. One case demonstrated persistent graft survival 24 years post-implantation without signs of chronic immune activation[46], although cognitive decline and reduced L-DOPA responsiveness emerged after 14 years, possibly due to host-to-graft $\alpha$-SYN transmission.

Unilateral transplantation of hfVM tissue into the putamen of PD patients restored DA function (evidenced by increased $^{18}$F-DOPA uptake) and improved rigidity, bradykinesia, and L-DOPA-induced motor fluctuations, mainly contralateral to the graft[48]. Early dyskinesias often subsided as the graft matured. Recovery remained incomplete, reflecting variability in graft survival, reinnervation, and ongoing host DA, suggesting bilateral implantation may be needed for optimal long-term benefit.

The TransEuro trial investigated the effects of hfVM transplants in 11 patients with early-stage PD over a three-year period, using imaging ($^{18}$F-DOPA, DAT, and serotonergic markers) and motor assessments (UPDRS III) alongside 12 months of immunosuppressive therapy. Overall, the transplants did not produce a clear improvement in motor function compared to controls, although some patients showed a positive relationship between graft survival and DA PET signals, with outcomes differing by surgical site and device used. Secondary outcomes indicated slight reductions in L-DOPA dosage and OFF time, and three patients experienced mild, non-disabling graft-induced dyskinesias. Adverse events were frequent but mostly minor, with no deaths or long-term disabilities reported[126].

Despite encouraging findings, inconsistencies across trials have been reported, often due to differences in surgical technique, blinding, and outcome measures. A major limitation is the potential for immune rejection of allogeneic grafts, which can compromise long-term survival and functional performance[129]. Postmortem studies from additional patients revealed significant increases in striatal $^{18}$F-DOPA uptake and reduced motor fluctuations after transplantation, reinforcing clinical relevance[127].

In addition to restoring DA neurotransmission, preclinical studies indicate that fVM-derived neural stem cells may exert ancillary neuroprotective effects, including the promotion of hippocampal neurogenesis and sustained post-transplant protection[130]. A major limitation, however, is the susceptibility of grafted neurons to host-to-graft $\alpha$-SYN propagation. Postmortem analyses have shown that transplanted neurons can develop LB-like inclusions years after implantation[131-136]. Experimental

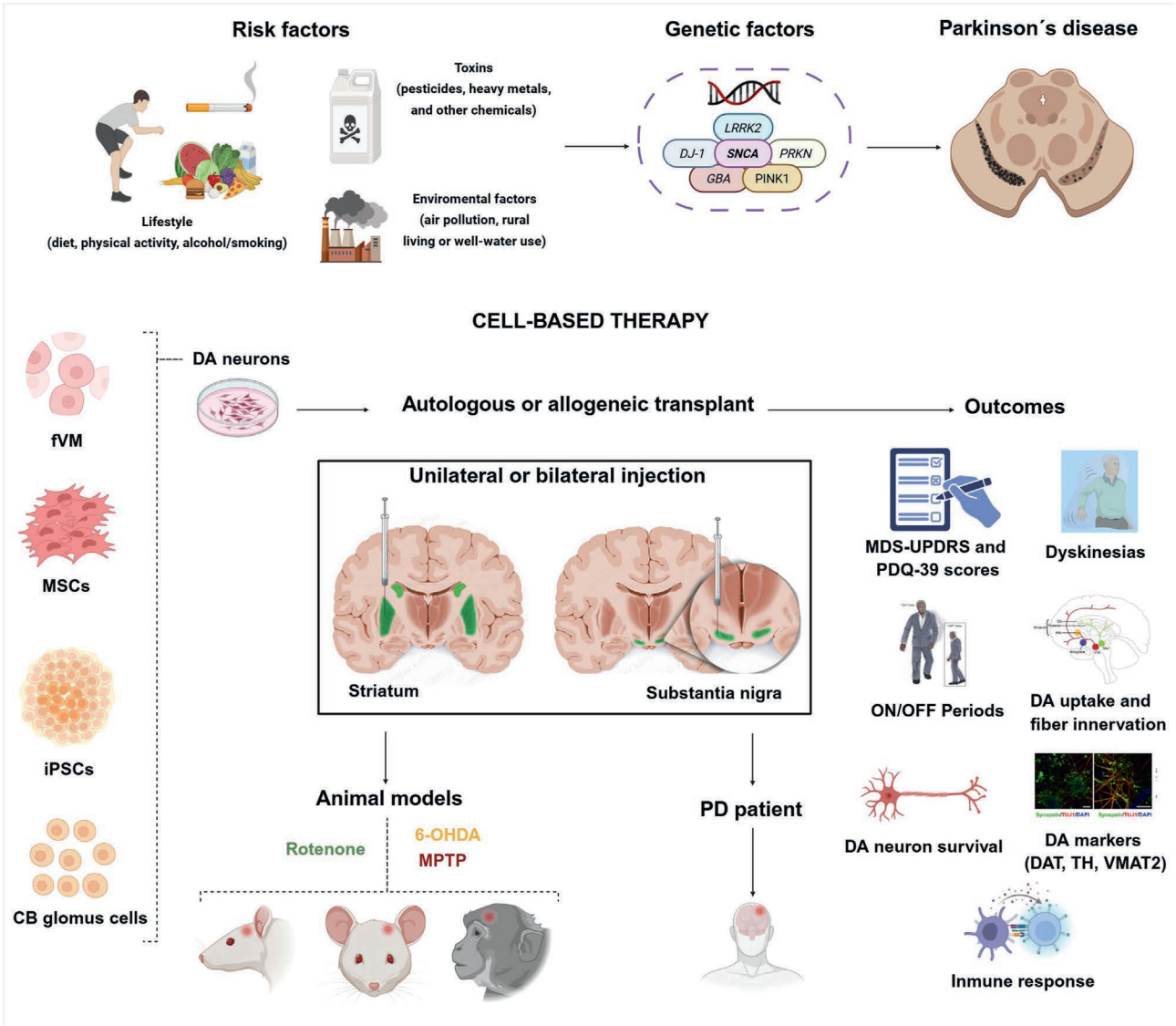


**Figure 4** Cell-based regenerative interventions in Parkinson's disease. Parkinson's disease (PD) is influenced by lifestyle factors, environmental toxins, and genetic mutations, including *SNCA*, *LRRK2*, *PRKN*, *PINK1*, *DJ-1*, and *GBA*. Cell-based therapies aim to restore dopamine (DA) signaling using grafts derived from fetal ventral midbrain (fVM), human induced pluripotent stem cell (hiPSC)-derived DA neurons, mesenchymal stromal cells (MSCs), or carotid body (CB) glomus cells. These cells can be transplanted autologously or allogeneically into the striatum/caudate-putamen or substantia nigra. Their efficacy is evaluated in preclinical models and clinical trials, with outcomes including improved motor function, reduced ON/OFF periods, enhanced DA signaling, graft survival, and immune modulation.

work in 6-OHDA-lesioned rats demonstrated that host-derived human α-SYN can retrogradely transfer into grafted DA neurons without direct viral transfection, forming misfolded, proteinase K-resistant inclusions thereby providing mechanistic evidence for prion-like host-to-graft α-SYN propagation in PD[128]. These inclusions are thought to arise through mechanisms such as exosome-mediated transfer, receptor-dependent endocytosis, or direct membrane contact, which enable extracellular α-SYN to misfold and spread into previously healthy grafted neurons[128,137,138]. Such propagation disrupts proteostasis, impairs mitochondrial integrity, and ultimately compromises neuronal viability.

In addition to restoring DA neurotransmission, preclinical studies indicate that fVM-derived neural stem cells may exert additional neuroprotective effects, including the promotion of hippocampal neurogenesis and sustained protection after transplantation A major limitation, however, is the vulnerability of grafted neurons to host-to-graft α-SYN propagation. Postmortem analyses have revealed that transplanted neurons can develop LB-like inclusions years after implantation These inclusions are thought to arise through several mechanisms, such as exosome-mediated transfer, receptor-dependent endocytosis, or direct membrane contact, that enable extracellular α-SYN to misfold and spread into previously healthy grafted neurons[137-139]. Such propagation can compromise proteostasis, mitochondrial integrity, and neuronal viability.

To address this challenge, multiple strategies are under investigation. These include small-molecule inhibitors of α-SYN

**Table 1** FVM transplantation.

| Species | Animal model clinical stage | Transplantation site | Injection | Behavioral phenotype | Nigrostriatal and histological outcomes | Lewy body pathology | Ref. |
|---|---|---|---|---|---|---|---|
| Rat | 6-OHDA | Dorsal neostriatum | Unilateral | Amphetamine-induced rotation: ↓ rotational bias toward lesioned side (improved)<br>Spontaneous rotation: ↑ turning contralateral to transplant<br>Sensorimotor orientation: ↑ responsiveness contralateral to transplant<br>Sensorimotor asymmetry: ↓ asymmetry in T-maze and sensory attention | Not evaluated | Not assessed | [113] |
| Rat | 6-OHDA | 2 graft sites:<br>*Dorsal striatum* or *N. accumbens* prefrontal cortex or hippocampus | Unilateral | Striatal grafts restored rotations<br>*N. accumbens* grafts worsened bias<br>*P. cortex* or hippocampal grafts had no effect | Total neuron survival was similar across sites, but younger (E12) donor tissue and striatal sites:<br>↑ Number TH + neurons<br>↑ DA density<br>↑ A9/A10-like phenotypic differentiation | Not assessed | [114] |
| Rat | 6-OHDA | Multiple striatal grafts<br>A single SN graft | Unilateral | Multiple striatal grafts restored rotations more effectively than single SN grafts, showing better functional recovery | ↑ Striatal TH fiber density<br>↑ TH + neurons | Not assessed | [115] |
| Rat | 6-OHDA | Caudate-putamen | Unilateral | Not performed | ↑ Number of TH-immunoreactive neurons<br>↑ TH cell density<br>↑ TH fiber outgrowth | Not assessed | [116] |
| Rat | 6-OHDA | Striatum | Unilateral | ↓ Apomorphine-induced rotation | ↑ Striatal TH fiber density<br>↑ TH + neurons | Not assessed | [117] |
| Rat | 6-OHDA | Striatum | Unilateral | Not performed | Not evaluated | Transfer of hα-syn from host to graft | [128] |
| Rhesus monkey (*Macaca mulatta*) | MPTP | Caudate nucleus | Bilateral | ↓ Sedentary behavior | ↑ Catecholamine fiber density | Not assessed | [118] |
| New world monkey (Marmoset) | MPTP | Putamen | Unilateral | ↓ Amphetamine-induced rotation | ↑ Striatal TH fiber density | Not assessed | [119] |
| Green monkey (*Cercopithecus aethiops sabeus*) | MPTP | Caudate nucleus | Unilateral<br>Bilateral | Not performed | ↑ Striatal TH nerve density<br>↑ TH immunoreactive cells | Not assessed | [120] |
| Human | Severe PD | Putamen | Unilateral | ↓ Number of OFF-periods<br>↓ Limb rigidity & bradykinesia | ↑ Putaminal DA synthesis & storage | Not assessed | [97] |
| Human | Unspecified | Putamen | Bilateral | UPDRS, normal daily tasks, and self-rating scale improvements<br>Better upper extremity performance<br>↑ Lower extremity performance and H&Y scores | ↑ TH-positive neurons<br>Higher TH-cell density<br>Denser TH fiber outgrowth | Not assessed | [121] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Human | Unspecified | Post-commissural putamen | Bilateral | Improvement of motor function, daily living, UPDRS scores, and lower extremity performance<br>Resolution of dyskinesias, dystonia, and motor fluctuations | Graft survival<br>Dense TH-positive neurons<br>Extensive DA innervation<br>Seamless integration without host fiber sprouting | Not assessed | [122] |
| Human | Unspecified | Putamen | Bilateral | Improved UPDRS motor scores<br>Dyskinesias and motor fluctuations largely resolved | ↑ Putaminal DA uptake<br>Grafts integrated structurally with host striatum<br>Robust DA innervation | Not assessed | [123] |
| Human | Severe PD | Putamen | Bilateral | Improved UPDRS and Schwab & England OFF-scores (mainly in younger patients) | ↑ Putaminal DA uptake<br>85% graft survival | Not assessed | [124] |
| Human | Severe PD | Post-commissural putamen | Bilateral | Improved UPDRS motor off-period performance | ↑ Putaminal DA uptake<br>↑ TH immunoreactivity in grafts | Not assessed | [125] |
| Human | Severe PD | Putamen | Unilateral | Gradual loss of L-DOPA response<br>Progressive loss of motor function<br>Cognitive decline starting at 14 years post-transplantation | ↑ TH + neurons in grafts<br>Complete TH reinnervation<br>↑ TH fiber density<br>Absence of inflammatory response<br>Widening of the lateral ventricles & severe medial temporal lobe atrophy | α-Syn & ubiquitin inclusions (~12% of transplanted cells) | [46] |
| Human | Severe PD | Post-commissural putamen<br>SN | Bilateral | Improvement in total & motor UPDRS scores | Restoration of putaminal DA uptake<br>↑ Graft reinnervation with TH fibers | Not assessed | [47] |
| Human | Severe PD | Caudate & putamen<br>Putamen only | Unilateral<br>Bilateral | ↑ Health-related quality of life | ↑ DA uptake in some patients | Not assessed | [48] |
| Human | Moderate PD | Putamen | Bilateral | No clear UPDRS-III benefit overall<br>↓ L-DOPA equivalent daily dose<br>↓ OFF-state duration<br>↑ Dyskinesias | Increased or stabilized putaminal DA activity | Not assessed | [126] |
| Human | Severe PD | Caudate & putamen<br>Putamen only | Bilateral | Improvement of UPDRS score<br>Independence in all activities of daily living<br>↓ Dyskinesias<br>Withdrawal of DA medication | Normalization of DA uptake | Not assessed | [127] |

aggregation[140,141], pharmacological inducers of autophagy such as trehalose and rapamycin analogs[58,62], and passive immunization approaches targeting extracellular $\alpha$-SYN[59,60]. Passive immunization, in particular, offers advantages due to its high specificity, long half-life, and ability to neutralize extracellular $\alpha$-SYN without imposing significant cellular stress or immune activation[126]. Complementary strategies involve preconditioning grafts to enhance their intrinsic resilience, for example, by overexpressing molecular chaperones chaperones[142], lysosomal regulators[143], or proteasome activators[144] to bolster proteostatic and mitochondrial defenses against host-derived pathology.

Despite these advances, the widespread clinical use of fVM tissue remains limited by ethical and logistical constraints. Fetal tissue availability is restricted, and strict regulations hinder scalability. Accurate identification of A9 versus A10 DA neuron subtypes is critical for ensuring proper graft functionality. Thompson et al. used TH-green fluorescent protein (GFP) transgenic mice to distinguish these subtypes *via* GIRK2 (G-protein-regulated inward-rectifier potassium channel 2) and calbindin markers, thereby improving donor tissue characterization[145]. Generating defined yet heterogeneous DA neuron populations may support appropriate circuit integration and functional neurotransmission.

In summary, fVM-derived DA neuron grafts demonstrate long-term survival, integration, and clinical benefit. However, key obstacles remain, including immunogenicity, $\alpha$-SYN pathology, and donor tissue limitations. Future protocols should focus on refining graft composition, enhancing resilience to host pathology, and ensuring durable integration to fully realize the therapeutic potential of fVM-based or next-generation regenerative approaches in PD.

### *3.2. Implantation of human induced pluripotent stem cell-derived dopamine neurons*

hiPSCs provide a renewable, scalable, and ethically acceptable source of DA neurons for treating PD. Derived from a patient's own somatic cells, hiPSCs retain the donor's genetic identity, reducing the risk of immune rejection and potentially eliminating the need for long-term immunosuppression. They can be directed to differentiate into midbrain-specific DA neurons that closely mimic the molecular and functional properties of native SN neurons[146-148]. Their compatibility with standardized manufacturing protocols and suitability for cryopreservation further support their clinical utility and potential for personalized regenerative therapies.

Historically, fVM tissue represented the primary source for DA grafts. However, its limited availability, variability, and ethical concerns have restricted clinical application. In this context, hiPSCs provide virtually unlimited availability, greater reproducibility, and fewer ethical and logistical constraints. These features make hiPSC-derived DA neurons a promising and sustainable alternative for disease-modifying cell-based therapies in PD. Floor plate-based differentiation protocols enable efficient generation of mature, functional DA neurons capable of survival, integration, and functional restoration following transplantation[149,150]

Pioneering work established that somatic fibroblasts from patients with idiopathic PD can be reprogrammed into functional DA neurons using doxycycline-inducible lentiviral vectors[67]. Activation of Wnt and fibroblast growth factor (FGF) 8 signaling remains the gold standard for midbrain DA specification[38], though newer approaches employing small-molecule inhibition of transforming growth factor $\beta$ (TGF-$\beta$), bone morphogenetic protein, and glycogen synthase kinase 3$\beta$ have enhanced differentiation efficiency and maturation[151]. Nevertheless, graft failure often results from challenges in maintaining DA neuron identity post-transplantation rather than intrinsic vulnerability of the grafted cells[152].

Preclinical studies in rodent and primate models have established the safety and efficacy of hiPSC-derived DA neuron transplantation. In 6-OHDA-lesioned mice, mRNA-reprogrammed human fibroblasts differentiated into DA-like neurons that survived in the SN, promoted axonal outgrowth into target regions (*e.g.*, dorsolateral striatum, prelimbic cortex), and alleviated motor impairments for up to 12 months, despite some apoptotic loss among grafted neurons[39]. In 6-OHDA-lesioned rats, patient-specific hiPSC-derived DA neurons survived long-term without inducing immune responses or tumor formation and reduced amphetamine- and apomorphine-induced rotational behavior[153]. Protein-based reprogramming approaches further enhanced TH $^+$ neuron survival and motor recovery[154], while co-delivery of metabolism-regulating miRNAs improved graft quality and integration[42].

Autologous transplantation of hiPSC-derived DA neurons has been shown to restore motor function and promote dense $TH^+$ innervation in 6-OHDA-lesioned rats, with no tumorigenicity detected up to 26 weeks post-grafting[42]. Clinical-grade, non-tumorigenic DA progenitors implanted into the striatum of 6-OHDA-lesioned rats and MPTP-lesioned monkeys resulted in improved DA viability, nigrostriatal connectivity, and behavioral performance, without adverse effects[40]. iPSC-derived neurons from healthy and PD donors enhanced spontaneous activity, cell survival, and DA uptake in MPTP-treated cynomolgus monkeys[41]. Comparable outcomes were observed in MPTP-exposed macaques following unilateral transplantation of autologous iPSC-derived DA neurons, leading to restored DA uptake, elevated DOPAC levels, and improved motor function[72,155].

In rhesus monkeys, autologous transplantation of iPSC-derived midbrain DA neurons, performed 1−3 years after MPTP infusion, alleviated motor and mood symptoms, enhanced DA activity, and did not induce persistent immune activation[43]. Major histocompatibility complex (MHC)-matched allogeneic grafts showed reduced microglial and lymphocyte infiltration, enhancing survival of iPSC-derived DA neurons in *Macaca fascicularis*[156]. In green monkeys, bilateral intracranial delivery of human parthenogenetic stem cells into the caudate, putamen, and SN led to robust DA neuron differentiation, increased striatal $TH^+$ innervation, and improved behavioral outcomes over a 12-month period, with no signs of dyskinesia[157]. Key preclinical findings are summarized in Table 2[39-13,49-51,72,153-157].

Despite these advances, clinical implementation remains in early stages. The first completed clinical trial involved bilateral implantation of hiPSC-derived DA neurons into the putamen of a PD subject, without immunosuppression. $^{18}$F-DOPA PET/CT scans showed moderate presynaptic DA terminal activity near the implantation site, with sustained clinical improvements over 24 months in MDS-UPDRS III, PD questionnaire-39, and self-reported OFF periods[50].

Ongoing trials aim to validate these early results. In 2018, Kyoto University Hospital initiated a single-arm, open-label Phase I/II study involving bilateral putaminal transplantation of hiPSC-derived DA progenitors[51]. At 24 months, the treatment yielded improved motor outcomes and increased $^{18}$F-DOPA uptake, supporting the safety and efficacy of this allogeneic approach[49]. A

**Table 2** hIPSc-derived DA neuron transplantation.

| Species | Animal model clinical stage | Transplantation site | Injection | Behavioral phenotype | Nigrostriatal and histological outcomes | Lewy body pathology | Ref. |
|---|---|---|---|---|---|---|---|
| Mouse | 6-OHDA | SN | Unilateral | ↓ Amphetamine-induced rotation | ↑ Graft axonal outgrowth in several brain regions<br>↑ Apoptotic activity<br>↓ Number of TH + neurons | Not assessed | [39] |
| Rat | 6-OHDA | Dorsolateral striatum | Unilateral | ↓ Rotational asymmetry<br>No improvement in cylinder or stepping | Surviving midbrain-like DA neurons<br>Limited axonal outgrowth<br>Mild gliosis<br>No inclusions/tumors | Not assessed | [153] |
| Rat | 6-OHDA | Striatum | Unilateral | Motor recovery with high and optimal NPC doses | Stable grafts at optimal dose<br>Survival of TH + midbrain-like neurons<br>Poor survival of terminal cells<br>No tumors except at high dose | Not assessed | [154] |
| Rat | 6-OHDA | Striatum | Unilateral | ↓ Rotational behavior | ↑ Number of TH + neurons<br>Widespread $hNCAM^+$ innervation<br>Absence of both teratomas & rosettes | Not assessed | [42] |
| Rat | 6-OHDA | Striatum | Unilateral | ↓ Methamphetamine-induced rotational behavior | ↑ Striatal TH nerve density<br>↑ TH immunoreactive neurons | Not assessed | [40] |
| Cynomolgus monkey | MPTP | Putamen | Unilateral | Not performed | ↑ TH + neuron survival<br>Lack of intracranial hemorrhage<br>Absence of inflammation | Not assessed | [40] |
| Cynomolgus monkey (*Macaca fascicularis*) | MPTP | Putamen | Bilateral | Improved neurological/motor function<br>Recovery of spontaneous movements | ↑ Putaminal DA uptake<br>↑ Survival of grafted DA neurons<br>↑ TH fiber innervation<br>No immune response or tumor formation | Absence of LBs | [41] |
| Cynomolgus monkey | MPTP | Putamen | Unilateral | No significant changes in motor behavior | Surviving midbrain-like DA neurons<br>Extensive TH fiber reinnervation<br>Presence of mature synapses<br>Normal mitochondrial morphology<br>Minimal microglial activation<br>Lack of tumor formation | Not assessed | [72] |
| Cynomolgus monkey | MPTP | Caudate nucleus<br>Putamen | Unilateral | Partial recovery of PD symptoms | ↑ TH-immunopositive neurons in grafts<br>Extensive DA fiber innervation<br>↑ Local DA & DOPAC levels<br>↑ Synaptophysin immunoreactivity<br>No microglial activation | Not assessed | [155] |
| Rhesus monkey (*Macaca mulatta*) | MPTP | 7 tracts:<br>3 × Caudate<br>3 × Putamen<br>1 × SN | Unilateral | ↓ Signs of mood-related disorders<br>Autologous grafts:<br>↑ Clinical rating & fine motor skills<br>↓ Mood-related deficits | Autologous grafts:<br>↑ $TH^+$ cells and putaminal DA<br>Extensive fiber outgrowth<br>Minimal immune response<br>Allogenic grafts: | Not assessed | [43] |

(*continued on next page*)

**Table 2** (*continued*)

| Species | Animal model clinical stage | Transplantation site | Injection | Behavioral phenotype | Nigrostriatal and histological outcomes | Lewy body pathology | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | Allogenic grafts:<br>No improvement<br>Mood deficits persist | ↓ $TH^+$ cells<br>Minimal fiber outgrowth<br>Strong immune/inflammatory response | | |
| Cynomolgus monkey (*Macaca fascicularis*) | MPTP | 6 tracts in the putamen | Unilateral | Not performed | ↑ Survival of DA neurons and reinnervation<br>↓ Iba-1+ and CD45+ cells<br>Transient neuroinflammation<br>Humoral response | Not assessed | [156] |
| Green monkeys (*Chlorocebus sabaeus*) | MPTP | 5 tracts:<br>1 × Ant. caudate<br>1× Post. caudate<br>1 × Ant. putamen<br>1 × Post. putamen<br>1 × SN | Bilateral | Low-dose hpNSCs improved parkinsonism:<br>↓ Number of Parkscores<br>↑ Healthy behavior scores<br>Lack of dyskinesia over 12 months | ↑ Striatal DA/HVA content<br>↑ Number of SN DA neurons<br>↑ Reinnervation with TH fibers<br>No evidence of tumor formation | Not assessed | [157] |
| Human | Unspecified | 2 tracts in the putamen | Bilateral sequential | Improvement in MDS-UPDRS III & PDQ-39 scores<br>↓ L-DOPA requirement<br>Absence of dyskinesias | Moderate restoration of putaminal DA uptake<br>Graft survival<br>No adverse histopathological findings | Not assessed | [49] |
| Human | Unspecified | Putamen | Bilateral | Improved MDS-UPDRS III<br>Mild H&N improvement<br>Stable PDQ-39<br>Nearly unchanged L-DOPA dose | DA progenitors engrafted and matured into TH + neurons<br>↑ Putaminal DA uptake<br>Moderate DA restoration<br>No tumor formation or inflammation | Not assessed | [50, 51] |

parallel open-label trial (NCT06145711), conducted by Shanghai East Hospital and XellSmart Biomedical, is currently evaluating unilateral autologous transplantation of iPSC-derived DA precursors into the globus pallidus interna in three PD patients.

In summary, hiPSC-derived DA neurons represent a promising regenerative therapy for PD. Their scalability, personalized nature, and compatibility with advanced differentiation protocols (summarized in Table 3[38,39,42,67,146,151,154,158-171]), make them a viable alternative to fetal-derived sources[38,39,50,67,146,152,154,158-171]. Preclinical studies support their functional efficacy, long-term survival, and integration into host circuits. However, challenges remain, particularly in optimizing neuronal identity, mitigating apoptotic cell death, and ensuring long-lasting safety. Both autologous and MHC-matched allogeneic approaches offer viable strategies for reducing immunogenicity. Ongoing clinical trials will be crucial in determining whether hiPSC-based therapies can fulfill their potential as a disease-modifying intervention in PD.

### *3.3. Mesenchymal stromal cell transplants*

MSCs are being investigated as supportive therapy for PD due to their immunomodulatory, anti-inflammatory, and neurotrophic properties[172]. While they do not inherently produce DA, MSCs secrete growth factors and cytokines that promote endogenous DA neuron survival, suppress neuroinflammation, and facilitate tissue repair. Their ease of isolation from adult tissues, low immunogenicity, and absence of tumorigenic potential make them a safe and ethically non-controversial therapeutic option[173].

MSCs are multipotent cells capable of differentiating into derivatives of the mesoderm, ectoderm, and endoderm. Unlike embryonic stem cells (ESCs) or iPSCs, MSCs are not associated with ethical concerns or the risk of teratoma formation, enhancing their suitability for clinical applications. As non-hematopoietic progenitors, MSCs can be harvested from a variety of sources, including bone marrow, adipose tissue, skin, peripheral blood, and placenta[174]. Several studies show MSCs can acquire neuronal-like phenotypes, expressing markers such as neuron-specific enolase, nestin, and glial fibrillary acidic protein[175,176]. Pharmacological stimulation with 3-isobutyl-1-methylxanthine and forskolin activates cyclic adenosine monophosphate (cAMP) signaling, enhancing neural differentiation and neuronal characteristics[177].

Preclinical evidence supports the neurorestorative potential of MSCs in PD. Intrastriatal transplantation of MSCs in MPTP-injected mice resulted in partial functional recovery and survival of $TH^+$ cells[178]. In 6-OHDA-lesioned rats, transplantation of rat bone marrow-derived MSCs (BM-MSCs) into the striatum or SN reduced rotational asymmetry, upregulated DA-associated markers (DA receptor 2, VMAT2, and DAT), and increased TH immunolabeling compared to sham controls[176,179]. These benefits are attributed to MSC-mediated neuroprotection *via* immunomodulation and trophic support[180]. Findings are summarized in Table 4[55,178-182].

However, low neuronal marker expression and poor graft survival remain major limitations. To overcome this, biodegradable, pharmacologically active microcarriers were combined with marrow-isolated adult multilineage inducible cells (a subpopulation of hMSCs) and implanted stereotaxically into the striatum of 6-OHDA-lesioned rats. This approach led to improved graft survival, behavioral recovery, and enhanced functionality of the nigrostriatal system[181]. Co-grafting low doses of MSCs with midbrain DA neurons has also improved outcomes in 6-hydroxydopamine (6-OHDA) hemiparkinsonian rats by reducing rotational behavior, enhancing spontaneous locomotion, and promoting graft survival and axonal reinnervation[182].

Clinically, an open-label pilot trial tested unilateral autologous MSC transplantation into the subventricular zone of PD patients, showing UPDRS improvements in OFF and ON states after 32 months, with no tumor formation or structural brain changes, and reduced dyskinesia in some cases[55]. Ongoing studies include a Phase I pilot trial (NCT02611167) and two Phase II randomized, double-blind trials (NCT04928287, NCT04506073) evaluating BM-MSCs as potential disease-modifying therapy.

A novel, unexplored avenue involves combining MSCs with biohybrid drugs exhibiting dual biological activity, potentially boosting homing efficiency and immunoregulatory functions[54]. Overall, MSCs show promise as a safe, multipotent, and neuroprotective cell-based approach for PD. Preclinical models demonstrate their ability to induce neuronal-like differentiation, increase DA marker expression, and improve motor function, while early clinical data suggest safety and potential benefit. Key challenges, including limited neuronal differentiation, low graft survival, and variable efficacy, may be addressed through biomaterial scaffolds, co-transplantation, and pharmacological enhancement. Results from ongoing randomized trials will determine their long-term feasibility and clinical utility.

### *3.4. Intracranial delivery of carotid body glomus cells*

CB glomus cells represent a neuroprotective approach for PD owing to their dual capacity to produce DA and secrete high levels of glial cell line-derived neurotrophic factor (GDNF)[183,184]. Although lacking DAT expression, these cells display strong resistance to neurotoxic insults and exert trophic effects that support neuronal survival, reinnervation, and functional recovery through both neurochemical and non-canonical mechanisms[183].

Preclinical studies in rodent and non-human primate models demonstrate robust antiparkinsonian effects of CB grafts. In both mice and monkeys, CB cell transplantation conferred resistance to MPTP-induced DA neurodegeneration despite lacking DAT expression[183,185]. In MPTP-lesioned mice, striatal CB implants improved rearing behavior, preserved nigrostriatal pathway integrity, and significantly upregulated GDNF mRNA expression without triggering detectable inflammatory responses[186].

Similarly, in 6-OHDA-lesioned rats, striatal CB grafts ameliorated motor deficits in a subset of animals, prevented ongoing DA neuron loss, promoted DA terminal sprouting, and enhanced neurotrophic signaling[183]. Transplantation of CB cell aggregates further alleviated motor and sensory impairments, enhanced calcium-dependent DA release, and induced host striatal reinnervation[187]. Table 5[52,53,183-188] offers a consolidated summary of the most relevant preclinical and clinical findings outlined in the preceding section.

CB aggregate grafts into the putamen of cynomolgus monkeys improved motor performance, increased DA uptake in the grafted striatum, and increased the number of $TH^+$ neurons expressing GDNF[188]. In MPTP-treated *Macaca fascicularis*, unilateral CB cell transplantation targeted to the putamen significantly ameliorated tremor, bradykinesia, akinesia, and postural instability, accompanied by enhanced $TH^+$ reinnervation and greater survival of glomus cells[185].

Clinical evidence from a phase I/II blinded trial indicated that CB autotransplantation improved total UPDRS scores in several patients, with minimal OFF-period dyskinesias observed between 6 and 12 months post-surgery[52,53]. Follow-up at 3 years indicated

**Table 3** Strategies for DA lineage differentiation.

| Cell source | Reprogramming/differentiation strategy | Cell type | Neuronal induction/differentiation method | DA markers | Maturation period | Ref. |
|---|---|---|---|---|---|---|
| hESCs (HS980, HS401)<br>hiPSCs (SM55, SM56) | Not applicable (direct conversion) | Ventral midbrain DA neurons | Direct induction: dual SMAD inhibition, ROCK inhibitor, DMH1 inhibition, CHIR99021, *β-mercaptoethanol*, and SB431542<br>48-h RA pulse<br>SHH pathway activation (SAG)<br>Mechanical dissociation at 9 DDC<br>Terminal differentiation with BDNF, GDNF, and AA<br>ROCK inhibitor used during plating and passaging | ASCL1, CLSTN2, FOXA2, LMX1A, NURR1, OTX2, PITX3, PTPRO, and TH | *In vitro:*<br>∼40−45 days<br><br>*In vivo:*<br>∼7 months post-transplantation | [38] |
| Human dermal fibroblasts (from a 28-year-old donor) | mRNA-based reprogramming using a StemMACS kit with OCT4, SOX2, KLF4, LIN28, C-MYC, NANOG, and GFP mRNAs | Midbrain DA neurons (SNpc and VTA subtypes) | A commercial 3-step kit protocol:<br>Floor plate specification (10 days), expansion (10 days)<br>Neuronal maturation (≥5 days)<br>Cells were harvested at day 26 for transplantation<br>BDNF, GDNF, DAPT, ascorbate plated with PDL and laminin | Calbindin, DAT, EN2, FOXA2, GIRK2, LMX1A, NeuN, NURR1,<br>OTX2, PITX3, and TH | *In vitro*: up to day 26<br><br>*In vivo*:<br>1−12 months post-transplantation | [39] |
| Autologous human dermal fibroblasts | iPSC reprogramming | Midbrain DA progenitor cells | Differentiation to mDAPs under GMP conditions:<br>Directed toward SNpc fate<br>Endpoint Day 28<br>Quercetin treatment to eliminate undifferentiated cells<br>Functional validation: DA secretion, electrophysiology, TH expression | hNCAM and TH | *In vitro*:<br>28 days<br><br>*In vivo* (6-OHDA rat model):<br>28 days | [42] |
| Human dermal fibroblasts from iPD patients | DOX-inducible lentiviral transduction of OCT4, SOX2, and KLF4 (±c-MYC)<br>Cre-lox excision for factor-free hiPSCs | DA neurons | EB-based differentiation or MS5 stromal co-culture + BMP antagonist noggin<br>Neural induction with FGF2, FGF8, and SHH<br>Terminal differentiation by growth factor withdrawal | TH and TUJ1 | ∼24 days for reprogramming +<br>8 days for terminal differentiation | [67] |
| Human dermal fibroblasts (skin biopsy from a healthy 28-year-old woman) | Reprogramming of human fibroblasts into hiPSCs using the StemMACS iPSC mRNA Reprogramming kit over 14 days | Midbrain DA neurons | Floor-plate-based protocol using the PSC DA neuron differentiation kit<br>Dual SMAD inhibition for neural induction<br>WNT and SHH pathway activation for midbrain patterning<br>Maturation with BDNF, GDNF, AA, cAMP, DAPT, and TGF-β3 | EN2, FOXA2, LMX1A, NURR1, OTX2, PITX3, and TH | *In vitro*:<br>22−26 days<br><br>*In vivo*:<br>9−12 months post-transplantation | [146] |
| ESCs iPSCs<br>TiPSCs | Sendai virus to establish TiPSC clones | Midbrain DA neurons | CTraS method: a cocktail of small molecules (SB431542, DM, and CHIR99021) to accelerate differentiation<br>CdNS-MD protocol: a Modification of the CTraS method that induces a midbrain DA identity using SHH and FGF-8<br>Maturation phase: BDNF + GDNF + RA + DAPT | PAX6, SYNAPSIN1, and TH | *In vitro*:<br>30−40 days | [151] |
| hESCs (H1, H9)<br>hiPSCs (2C6, SeV6) | Not applicable (direct conversion) | Midbrain-like DA neurons | Direct induction: Floor plate-based strategy<br>Directed differentiation *via* dual SMAD inhibition + SHH (C25II, PMA), FGF8, and CHIR99021<br>Cultured in Neurobasal B27 medium + AA, BDNF, GDNF, TGFβ3, and db-cAMP<br>CHIR added from Days 3−11 | Calbindin, DAT, FOXA2, GIRK2, LMX1A, NURR1, OTX2, and TH | *In vitro*:<br>25−80 days<br><br>*In vivo*:<br>18−20 weeks | [152] |
| hiPSCs (protein-based, Retroviral, lentiviral) and hESCs (H9, HSF-6) | Protein-based reprogramming (OCT4 + SOX2 + KLF4 + MYC) fused to a cell-penetrating peptide | Midbrain-like DA neurons | Neural induction: co-culture on MS5-SHH feeder cells + ITSA (+bFGF)<br>Midbrain patterning: co-culture on MS5-<br>SHH + ITSA + bFGF + SHH + FGF8<br>Terminal differentiation: ITSA + BDNF + GDNF + cAMP | Calbindin, DAT, EN1, GIRK2, LMX1A, LMX1B, Nurr1, TH, and VMAT2 | *In vitro*:<br>15 days<br><br>*In vivo*:<br>8 weeks post-transplantation | [154] |
| Mouse and human fibroblasts (from healthy<br>and PD donors) | Not applicable (direct conversion) | iDA neurons | Direct reprogramming via lentiviral overxpression of MASH1 (ASCL1), NURR1, and LMX1ACultured in neuronal induction medium (DMEM/F12 + supplements) + DOX for 6−24 days<br>No intermediate progenitor stage | ALDH1A1, AADC, D2 R, DAT,<br>TH, TUJ1, and VMAT2 | 12−24 days | [158] |

| | | | | | | |
|---|---|---|---|---|---|---|
| hiPSCs | Not applicable (direct conversion) | Midbrain DA neurons | Three induction protocols:<br>1. Dual inhibitor (SB431542 and DM)<br>2. Dual inhibitor plus SHH and FGF8<br>3. CHIR99021, SHH, and FGF8 combined protocol<br>Final maturation with N2B27, cAMP, BDNF, GDNF, and AA | DAT, FOXA2, Nestin, PITX3, SOX2, and TH | *In vitro*: up to 41 days<br><br>Neuronal maturation: 33−41 days | [159] |
| Keratinocytes (plucked hair) and PBMCs (blood) from same donor | Reprogramming to hiPSCs using a Sendai viral vector (non-integrating) | Midbrain DA neurons | 2D protocol (Kriks et al., 2011):<br>Induction: LDN193189, SB431542, CHIR99021, SHH, C25II, PMA, and FGF8<br>Medium transition: KSR to N2<br>Maturation: BDNF, GDNF, AA, db-cAMP, TGF$\beta$3, and DAPT<br><br>3D protocol (Jo et al., 2016):<br>EB formation: 4 days<br>Induction: SB431542 or noggin, and CHIR99021<br>Patterning: SHH C25II and FGF8<br>Steps: Embedding in Matrigel and culturing on an orbital shaker<br>Maturation: BDNF, GDNF, AA, and db-cAMP | FOXA2, LMX1A, NURR1, and TH | 2D:<br>∼30 days<br><br>3D:<br>∼39 days | [160] |
| MEFs | Not applicable (direct conversion) | iDA neurons | Direct transdifferentiation of post-mitotic MEFs by lentiviral overexpression of the transcription factors ASCL1, NURR1, and LMX1A<br>DOX-induced expression of transcription factorsNeuronal-inducing medium (DMEM/F12 + insulin, transferrin, selenium, progesterone, and putrescine)<br>No pluripotency stage involved | EN1, FOXOA1, FOXOA2, TUJ1, TH, and VMAT2 | *In vitro*:<br>14 days post-induction | [161] |
| hESCs (H9, H7)<br>hiPSCs (C4, N3) | Reprogramming using episomal vectors carrying with (OCT4, SOX2, KLF4, and L-MYC) and 2 microRNA clusters (miR-302s and 200c) | Midbrain DA progenitors and neurons | Directed differentiation using dual-SMAD inhibition + SHH and WNT activation<br>Physical confinement *via* "spotting" method<br>Maturation factors include BDNF, GDNF, and AA | LMX1A, FOXA2, and NURR1 | ∼28 days | [162] |
| Human dermal fibroblasts from PD patients with mutations in PARK2 or PARK8 genes | Lentiviral and Sendai virus-based reprogramming to iPSCs | DA neurons | Three-step 2D protocol:<br>Step 1 (Days 0−14): dual SMAD inhibition using noggin, SB431542, DM to generate early neural progenitors<br>Step 2 (Days 14−24): Ventral midbrain patterning using SHH, FGF8, and PMA to produce midbrain neuronal progenitors<br>Step 3 (Days 24−38+): Maturation using Neurobasal medium with B27 supplement, BDNF, GDNF, AA, and forskolin to obtain postmitotic DA neurons | CALB1, DAT1, SOX6, Synaptophysin, and TH | Minimum:<br>38 days<br><br>Full maturation: up to 65 days | [163] |
| hESCs (H9)<br>hiPSCs (C001, C002, C005) | Not applicable (direct conversion) | A9 DA neurons | Direct induction: dual-SMAD inhibition (SB431542, DM)<br>SHH and WNT activation (PM, CHIR)<br>Maturation with BDNF, GDNF, TGF$\beta$3, db-cAMP, and DAPT<br>Optimized timing and concentration for iPSCs | ALDH1A1, Calbindin, Corin, EN1, FOXA2, LMX1A, LMX1B, NURR1, and TH | 60−70 days | [164] |
| Gingival and dermal fibroblasts (healthy and PD patients) | Sendai virus reprogramming to obtain hiPSCs for pharmacological Induction | DA neurons | Pharmacological protocol:<br>Induction phase: dual SMAD inhibition (LDN193189 + SB431542) + SHH + PMA + CHIR99021<br>Maturation phase: BDNF + GDNF + TGF$\beta$3 + cAMP + AA<br>Direct conversion with AAV viral vector protocol:<br>AAV-mediated expression of transcription factors (LMX1A, NURR1, and PITX3)<br>Differentiation medium: BDNF, GDNF, TGF$\beta$3, db-cAMP, AA, and DAPT | AADC, DAT, LMX1a, NURR1, PIXT3, and TH | ∼20−25 days | [165] |

(*continued on next page*)

**Table 3** (*continued*)

| Cell source | Reprogramming/differentiation strategy | Cell type | Neuronal induction/differentiation method | DA markers | Maturation period | Ref. |
|---|---|---|---|---|---|---|
| hESCs (H9, H1)<br>hiPSCs (DANi002C) | Not applicable (direct conversion) | Mesencephalic DA neurons | Days 0−9: dual-SMAD inhibition (SB431542, LDN193189), CHIR99021, SHH, SAG for floor plate induction<br>Days 9−11: FGF8 for midbrain patterning<br>Days 11−16: FGF8, AA, LM22A4, BDNF, db-cAMP, GDNF, and DAPT<br>Days 16−30: same supplements, plated on poly-L-ornithine and laminin<br>Y-27632 on days 0, 11, 16, and 24 | CALB1, EN1, FOXA2, GIRK2, LMX1A, OTX2, and TH | *In vitro*: up to 62 days<br>*In vivo*: behavioral and histological assessments at 8, 18, and 26 weeks post-transplantation | [166] |
| hiPSCs (201B7) | Not applicable (direct conversion) | Midbrain DA neurons | Neurosphere-based protocol:<br>CTraS induction (Days 0−5): SB431542, DM, CHIR99021<br>Neurosphere formation (days 5−8): SB431542, Y27632, and bFGF<br>Ventral midbrain patterning (day 8+): CHIR99021 and PMA<br>Terminal differentiation (day 19+): BDNF, GDNF, AA, db-cAMP, TGF-$\beta$3, DAPT, and CHIR99021 (Day 19 only) | ALCAM, Calbindin, Corin, FOXA2, GIRK2, LMX1A, LRTM1, NURR1, PITX3, and TH | *In vitro*:<br>∼36 days (19 days to neurosphere + 17 days post-plating)<br>*In vivo*:<br>16 weeks post-transplantation | [167] |
| Mouse and human PSCs (ESCs, iPSCs) | Not applicable (direct conversion) | iDA neurons | One-step transcription factor induction with six midbrain-specific factors (ASCL1, NURR1, LMX1A, EN1, FOXA2, and PITX3) *via* piggyBac system<br>Maturation supported by BDNF and GDNF<br>Validated by marker expression, electrophysiology, and DA production | AADC, DAT, EN1, FOXA2, GIRK2, LMX1A, PITX3, TH, and VMAT2 | ∼3 weeks | [168] |
| hPSCs | Not applicable (direct conversion) | VM midbrain DA progenitors | Direct induction: dual SMAD inhibition (SB431542 + noggin), CHIR99021, SHH-C24II, and FGF8b<br>Maturation phase: BDNF + GDNF + AA + db-cAMP + DAPT | EN1, FOXA2, GIRK2, LMX1A,<br>OTX2, and TH | *In vitro*:<br>16−40 days<br>*In vivo*:<br>16−24 weeks | [169] |
| hEFs<br>HFL1 hFFs | Not applicable (direct conversion) | iDA neurons | Direct conversion *via* lentiviral overexpression of ASCL1, BRN2, MYT1L + LMX1A, and FOXA2<br>Converted cells were grown in N3 neural induction medium with DOX for at least 7 days | AADC, NURR1, and TH | 28−32 days | [170] |
| Human fetal lung fibroblasts (IMR-90) | Not applicable (direct conversion) | DA neuron-like cells | Direct chemical induction: VPA, RepSox, kenpaullone, forskolin, Y-27632, PMA, SHH, FGF-8b, bFGF, WNT1, and WNT5a<br>Maturation: Forskolin, kenpaullone, AA, SHH, FGF-8b, bFGF, BDNF, and GDNF | DAT, DDC, NURR1, and TH | 6−8 days induction +<br>7−14 days maturation | [171] |

Table 3. Glossary of abbreviations. AADC (Aromatic L-amino acid decarboxylase), AA (Ascorbic acid), AAV (Adeno-associated virus), ALCAM (Activated leukocyte cell adhesion molecule), ALDH1A1 (Aldehyde dehydrogenase 1 family member A1), Ascl1/MASH1 (Achaete-scute homolog 1), BDNF (Brain-derived neurotrophic factor), BMP (Bone morphogenetic protein), Brn2/POU3F2 (POU domain class 3 transcription factor 2), bFGF/FGF2 (Basic fibroblast growth factor), FGF8/8b (Fibroblast growth factor 8 isoforms), Foxa1/2 (Forkhead box proteins A1/A2), GDNF (Glial cell-derived neurotrophic factor), GFP (Green fluorescent protein), GIRK2 (G-protein-activated inwardly rectifying potassium channel 2), hESCs/hiPSCs/hPSCs (Human embryonic/induced pluripotent/pluripotent stem cells), hNCAM (Human neural cell adhesion molecule), ITSA (Insulin-Transferrin-Selenium-Sodium Pyruvate), KLF4 (Kruppel-like factor 4), Lmx1a/b (LIM homeobox transcription factors 1$\alpha$/1$\beta$), LRTM1 (Leucine-rich repeats and transmembrane domain protein 1), mDAPs (Midbrain dopaminergic progenitors), MEFs (Mouse embryonic fibroblasts), MYT1L (Myelin transcription factor 1-like), NeuN (Neuronal nuclei), Nurr1 (Nuclear receptor related 1 protein), OCT4 (Octamer-binding transcription factor 4), Otx2 (Orthodenticle homolog 2), PAX6 (Paired box protein 6), PBMCs (Peripheral blood mononuclear cells), Pitx3 (Paired-like homeodomain transcription factor 3), RA (Retinoic acid), RepSox/SB431542/LDN-193189/DMH1 (small-molecule pathway inhibitors), SHH/SHH-C24II (Sonic Hedgehog, isoform C24II), SNpc (Substantia nigra pars compacta), Sox2 (SRY-box transcription factor 2), TGF-$\beta$3 (Transforming growth factor $\beta$3), TH (Tyrosine hydroxylase), TiPSCs (T cell-derived induced pluripotent stem cells), TUJ1 (Neuron-specific class III $\beta$-tubulin), VMAT2 (Vesicular monoamine transporter 2), VPA (Valproic acid), VTA (Ventral tegmental area), Wnt1/5a (Wnt family members 1 and 5a), Y-27632 (ROCK inhibitor).

**Table 4** Mesenchymal stromal cell transplantation.

| Species | Animal model clinical stage | Transplantation site | Injection | Behavioral phenotype | Nigrostriatal and histological outcomes | Lewy body pathology | Ref. |
|---|---|---|---|---|---|---|---|
| Mouse | MPTP | Striatum | Unilateral | Significant motor recovery | Survival of MSCs in the striatum<br>Partial fiber restoration near grafts | Not assessed | [178] |
| Rat | 6-OHDA | Striatum | Unilateral | ↓ Attenuation of amphetamine-induced rotational behavior | Preservation of TH + neurons<br>↑ Striatal DA release<br>Partial restoration of DA markers (TH, DAT, VMAT2) in the striatum and SN | Not assessed | [179] |
| Rat | 6-OHDA | SN | Unilateral | Not performed | MSC survival in the SN<br>Stimulated subventricular zone neurogenesis<br>No rescue of nigral TH + neurons<br>Lack of DA differentiation | Not assessed | [180] |
| Rat | 6-OHDA | Striatum | Unilateral | ↓ Amphetamine-induced behavior (in DI-MIAMI + PAMs-NT3)<br>DI-MIAMI alone or PAMs-blank showed minimal or moderate improvement | Partial increase in ipsilateral SN TH + neurons<br>↑ Striatal TH fibers<br>TH expressed in grafted cells only with PAMs<br>↑ Expression of DA markers (DAT, TH, Nurr1) in DI-MIAMI + PAMs-NT3<br>Cells alone or PAMs-Blank showed minimal or no effect | Not assessed | [181] |
| Rat | 6-OHDA | Striatum | Unilateral | Partial motor recovery:<br>↓ Rotational behavior<br>↑ Spontaneous behavior<br>Modest forelimb improvement | SN TH number and striatal fiber density ↑ with low MSC co-grafting but ↓ with high MSCs<br>Graft volume unchanged<br>Reinnervation area and DA survival depended on MSC dose | Not assessed | [182] |
| Human | Unspecified | Subventricular zone | Unilateral | UPDRS scores improved in both "OFF" and "ON" periods<br>No change in H&Y scores<br>Slight reduction in L-DOPA dose<br>Marginal activities of daily living and dyskinesia improvement | Moderate putaminal DA restoration<br>BM-MSCs survived, integrated, and migrated to ipsilateral SN<br>Lack of parenchymal modifications without tumor development | Not assessed | [55] |

**Table 5** Carotid body glomus cell transplantation.

| Species | Animal model clinical stage | Transplantation site | Injection | Behavioral phenotype | Nigrostriatal and histological outcomes | Lewy body pathology | Ref. |
|---|---|---|---|---|---|---|---|
| Mouse | MPTP | Striatum | Unilateral | Not performed | CB grafts survived and integrated<br>Preservation of the nigrostriatal system<br>↑ Striatal GDNF expression in glomus cells<br>No tumor formation<br>Mild gliosis around the graft | Not assessed | [184] |
| Mouse | MPTP | Striatum | Unilateral | ↑ Number of rearing events | ↑ Striatal TH fiber innervation<br>↑ SN TH + neurons<br>Positive correlation between graft size and SN DA neuron protection<br>No changes in striatal or SN GFAP immunoreactivity<br>CB grafts survived and integrated, with no tumor formation | Not assessed | [186] |
| Rat | 6-OHDA | Striatum | Unilateral | Group I: normalized amphetamine/apomorphine responses<br><br>Group II: poor motor recovery with persistent DA supersensitivity | Production of neurotrophic factors<br>CB grafts survived long-term<br>Striatal reinnervation by ipsilateral SN and VTA neurons<br>↑ GDNF levels<br>DAT-negative | Not assessed | [183] |
| Rat | 6-OHDA | Striatum | Unilateral | Improved motor and sensorimotor function (amphetamine-induced rotations & whisker-mediated touch)<br>↓ Anxiety-like behavior (open field thigmotaxis) | CB grafts survived long-term<br>↑ Striatal TH-positive neurite outgrowth<br>Partial restoration of striatal DA | Not assessed | [187] |
| Cynomolgus monkey (*Macaca fascicularis*) | MPTP | Putamen | Unilateral | ↓ Tremor and bradykinesia<br>Recovery of balance and spontaneous activity<br>↓ Disability score (40%−50%)<br>↑ Improved fine motor skills<br>Persistent apomorphine-induced rotations | Grafted glomus cells survived<br>Extended TH + fibers<br>Induced robust ipsilateral striatal and caudate reinnervation | Not assessed | [185] |
| Cynomolgus monkey (*Macaca fascicularis*) | MPTP | 2 tracts into the post-commissural putamen | Unilateral Bilateral | Long-term improvement in global motor assessment and fine motor tasks (maximal at 6 months and stable up to 12 months) | ↑ Striatal $^{18}$F-DOPA uptake at 12 months<br>Total SN TH-positive neurons unchanged<br>Bilateral ↑ SN TH-positive neurons expressing GDNF | Not assessed | [188] |
| Human | Advanced | Patients 1−4: 3 putaminal targets (anterior, middle, posterior) | Bilateral | UPDRS "OFF" scores improved in most patients, peaking at 6 months | CB trophic support<br>Putaminal DA uptake not directly changed | Not assessed | [52] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Patients 5–6: added caudate nucleus target | | No OFF-period dyskinesias | Efficacy declined with patient age | | |
| Human | Advanced | Patients 1–4: 3 putaminal targets (anterior, middle, posterior) | Bilateral | Enhanced UPDRS III OFF-medication score (including bradykinesia and rigidity) | Higher CB integrity<br>Presence of TH + cells in transplanted tissue | Not assessed | [53] |
| | | Patients 5–6: added caudate nucleus target | | Improved Schwab and England, UPDRS II/IV scale scores<br>No OFF-period dyskinesias | Trend toward stabilized or slightly increased putaminal DA uptake | | |

that 50% of patients maintained improved motor function compared to baseline. Sustained DA uptake in the putamen was detected, with benefits achieved using fewer cells than typically required for fetal tissue transplantation, and without inducing OFF-period dyskinesia. However, donor CB glomus cell scarcity remains a major limitation.

Collectively, CB glomus cell transplantation represents a promising neuroprotective strategy for PD. By combining DA activity with potent trophic support, these grafts preserve the nigrostriatal system, promote reinnervation, and improve motor function, even in the absence of DAT-mediated DA recycling. Evidence from preclinical and clinical studies underscores their therapeutic potential, though interindividual variability and significant limited cell availability remain important obstacles. Advancing scalable CB glomus cell expansion, refining surgical delivery protocols, and conducting long-term efficacy studies will be essential to confirm durability of benefit. Addressing these challenges could position CB transplantation as a viable and clinically translatable neurorestorative therapy for PD.

### *3.5. Comparative insights into cell sources for Parkinson's disease therapy*

Neuroregenerative therapies for PD face persistent challenges, particularly in achieving durable graft survival and functional integration. Several cell sources have been explored, including fVM tissue, hiPSC-derived DA neurons, MSCs, and CB glomus cells, each exhibiting distinct strengths and limitations. Comparative evaluation highlights trade-offs between intrinsic functional maturity, scalability, immune compatibility, and ethical feasibility, building on the detailed characterization in Sections 3.1−3.4.

fVM grafts remain the benchmark for functional efficacy, demonstrating robust DA neuron characteristics. Clinical studies document transplanted A9-type DA neurons surviving for over two decades and contributing to sustained motor improvements[114,115,119,126,127]. Broader application is constrained by donor scarcity, variability in tissue quality, ethical considerations, and immunogenicity mediated by MHC class I/II expression[124].

hiPSC-derived DA neurons provide a renewable, scalable, and ethically acceptable alternative, with potential for autologous transplantation. Preclinical and early clinical studies show midbrain DA phenotypes and axonal extension[40,42,43,49,72,155]. Residual immunogenicity may arise from aberrant antigen expression or differentiation-induced MHC upregulation[56,57].

MSCs, derived from bone marrow, adipose tissue, placenta, or other sources, primarily act *via* paracrine mechanisms, secreting neurotrophic and immunomodulatory factors such as GDNF, brain-derived neurotrophic factor (BDNF), TGF-$\beta$, and IL-10[189,190]. Their immunoprivileged status and favorable safety profile make them suitable as adjunctive therapies alongside neuronal grafts[55].

CB glomus cells secrete DA and are enriched in GDNF, providing trophic support and resistance to neurotoxins[183-188], though limited DA reuptake due to absent DAT constrains functional efficacy. Clinical studies are limited[52,53], but their protective properties suggest utility in combinatorial strategies.

Overall, fVM grafts provide the strongest evidence of long-term survival and functional restoration, hiPSC-derived DA neurons offer versatility and scalability, and MSCs and CB glomus cells provide neurotrophic and immunomodulatory support that can complement primary neuronal grafts. These functional and

translational differences are summarized in Fig. 5 and Table 6, providing a comparative overview of cell sources for PD therapy.

### *3.6. Translational patterns, immune compatibility strategies, and decision-guiding trends among candidate cell therapies*

Building on the comparative framework of Section 3.5, translational patterns emerge across PD cell therapies. Methodological heterogeneity, including species differences, cell preparation protocols, transplantation methods, and outcome measures, precludes formal meta-analysis, yet convergent findings on graft longevity, functional impact, and clinical feasibility provide actionable guidance for future translation and highlight key translational barriers that need innovative solutions.

fVM grafts offer the clearest evidence of durable benefit, although ethical constraints, limited donor tissue, and the requirement for transient immunosuppression restrict broader application[46,47,124]. Immune rejection in fVM grafts primarily arises from MHC class I/II expression on donor cells, which can trigger host T cell-mediated responses, while microglial activation contributes to graft inflammation and long-term attrition. Standard systemic immunosuppressive regimens remain necessary, but innovative strategies are emerging to minimize peripheral exposure and directly address immune rejection. Localized delivery of slow-release immunosuppressants embedded within biomaterials at the graft site maintains graft tolerance while reducing systemic immunosuppression, exemplifying a synergistic approach that integrates cell therapy with engineered scaffolds to enhance graft survival.

hiPSC-derived DA neurons provide translational flexibility. Autologous hiPSC grafts are largely tolerated due to self-MHC expression, though aberrant antigen expression or differentiation-induced MHC upregulation can provoke immune responses[39,42,153,154]. Allogeneic hiPSC grafts, in contrast, risk conventional T cell-mediated rejection unless HLA-matched or engineered for immune evasion. Cutting-edge hypoimmunogenic hiPSC lines, created through targeted disruption of MHC class I/II genes and overexpression of immune checkpoint molecules such

A

| Therapy | Graft Survival | DA Release / Function | Immunogenicity | α-SYN Risk | Clinical Readiness |
|---|---|---|---|---|---|
| fVM grafts | 3 | 4 | 2 | 2 | 3 |
| hiPSC DA neurons | 4 | 4 | 4 | 3 | 3 |
| MSCs | 1 | 2 | 5 | 5 | 3 |
| CB glomus cells | 2 | 3 | 4 | 4 | 2 |

B

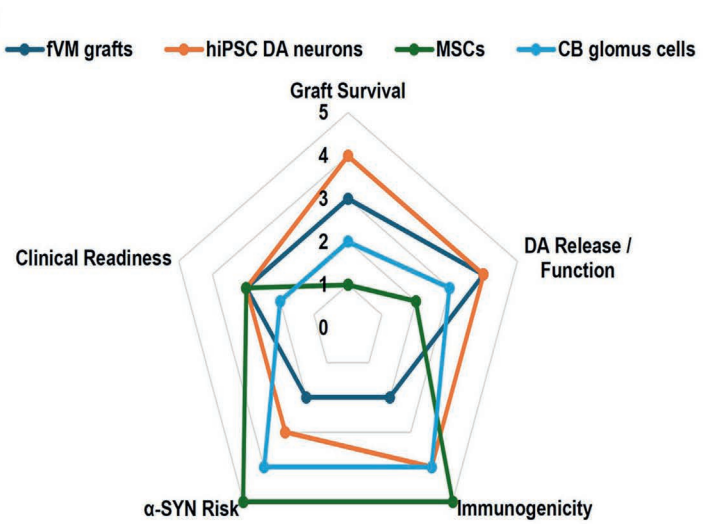


**Figure 5** Quantitative assessment of cell-based therapies for Parkinson's disease using outcome scores. (A) Summary table of efficacy measures from preclinical and clinical studies of fetal ventral midbrain (fVM) grafts, human induced pluripotent stem cell (hiPSC)-derived dopamine (DA) neurons, mesenchymal stromal cells (MSCs), and carotid body (CB) glomus cells. Measures are scored according to criteria established in this study. (B) Radar plot integrating five key outcome domains: graft survival, DA release and function, immunogenicity, α-synuclein (α-SYN) propagation risk, and clinical readiness. Scores are normalized on a 0−5 scale, with larger polygon areas indicating greater overall therapeutic effect based on the scoring system.

**Table 6** Comparison of cell sources for PD: mechanisms, characteristics, and clinical considerations.

| Therapy/cell type | Cell source | Therapeutic mechanism | Neuronal features | Graft survival | Immune compatibility | Tumorigenicity | Clinical status | Advantages | Limitations | Key challenges |
|---|---|---|---|---|---|---|---|---|---|---|
| fVM grafts | Fetal ventral mesencephalon | DA replacement, host integration<br>Moderate neurotrophic support | A9-type DA neurons<br>Synaptic integration | >20 years (human data) | Allogeneic, needs immunosuppression | None (post-mitotic) | Early trials (TRANSEURO) | Proven restoration<br>Long-term survival | Ethical/logistical issues<br>Immune rejection<br>α-Syn pathology | Standardization<br>α-Syn mitigation<br>Donor availability |
| hiPSC-derived DA neurons | Patient-derived iPSCs | DA replacement, personalized therapy<br>Minimal neurotrophic support | Midbrain DA phenotype<br>Synaptic integration | 2–3 years (preclinical and early clinical) | Autologous or HLA-matched | Low (validated protocols) | Phase I/II trials ongoing | Scalable<br>↓ Immunogenicity<br>Unlimited supply | DA identity maintenance<br>Apoptotic loss | Identity integration<br>Long-term safety |
| MSCs | Bone marrow<br>Skin<br>Blood<br>Adipose tissue<br>Placenta | Immunomodulation<br>High neurotrophic support (GDNF, BDNF) | Absent but with paracrine support | Poor without scaffolds | Immunoprivileged | None | Phase I/II trials ongoing | Safe<br>↓ Immunogenicity<br>Ethical | Limited DA production<br>Poor survival | Differentiation<br>Survival<br>Functional efficacy |
| CB glomus cells | Caroid body | DA + GDNF secretion<br>Very high neurotrophic support (GDNF-enriched) | DA-releasing ($TH^+$/DAT)<br>Paracrine support | Moderate (>3 years) | Autologous transplantation | None | Early preclinical and small clinical studies | Neurotoxin resistance<br>Trophic support | Limited DA release<br>Lack of DAT<br>Limited data | Scaling<br>Integration<br>Long-term outcomes |

as CD47, reduce recognition by host T and NK cells, enabling "off-the-shelf" transplantation[56,57]. HLA-matched hiPSC banks further improve compatibility while facilitating scalable clinical application. Combining these engineered cell lines with localized biomaterials represents a synergistic strategy that simultaneously tackles immune rejection and graft viability, providing a clear translational roadmap for future clinical trials.

Beyond primary neuronal grafts, cell types with paracrine activity, such as MSCs and CB glomus cells, act as supportive adjuncts rather than standalone DA replacements. Through secretion of neurotrophic and anti-inflammatory factors, these cells modulate local immune responses, enhance host microenvironments, and improve the integration and survival of co-transplanted DA neurons[174,183,184,191]. Strategic combinations of engineered neurons, supportive cell types, and biomaterial scaffolds thus constitute a multifaceted, synergistic strategy to overcome translational challenges in PD therapy, explicitly addressing both immune and functional limitations.

Overall, decision-making in clinical translation must explicitly balance efficacy, scalability, and immune compatibility. Selecting autologous, HLA-matched, or hypoimmunogenic engineered platforms based on patient needs and feasibility, coupled with localized immunomodulation and biomaterial-based delivery systems, provides a forward-looking framework to optimize graft viability and guide future clinical adoption in PD therapy.

### *3.7. Electrophysiological evidence of graft-host integration*

Histological and behavioral assessments have long served as the primary endpoints for evaluating cell transplantation in PD. However, electrophysiological analyses provide a critical benchmark for therapeutic success, offering direct proof that transplanted neurons are not only surviving but also forming functional synapses and participating in host circuitry. These studies establish functional integration as the *sine qua* non of restorative grafting.

*In vitro* patch-clamp recordings confirm that hiPSC-derived DA neurons fire both spontaneous and evoked action potentials, receive excitatory and inhibitory postsynaptic currents, and respond to afferent stimulation, hallmarks of mature neural connectivity[192,193]. Host afferents form functional synapses onto grafted neurons, while transplanted cells progressively acquire the electrophysiological properties required for participation in basal ganglia circuits.

*In vivo* studies further support these findings. In rodent PD models, transplanted DA neurons receive excitatory input from striatal and cortical projections while extending axons into striatal targets. Long-term recordings in 6-OHDA-lesioned immunodeficient mice revealed that hiPSC-derived DA neurons maintain stable firing patterns for more than one year, displaying tonic and burst firing characteristic of native nigral neurons[146].

Organoid-based models provide additional insight into network-level physiology. Human midbrain organoids derived from hiPSCs progressively express DA markers, exhibit activity-dependent DA release, and demonstrate synchronized bursting on multi-electrode arrays, indicative of coordinated neuronal activity[194]. Following transplantation, patch-clamp recordings from $EGFP^+$ organoid-derived neurons revealed spontaneous and evoked action potentials, afterhyperpolarization "sags," delayed inward rectification, and functional voltage-gated $Na^+$ and $K^+$ currents, confirming their maturation into electrophysiologically competent networks *in vivo*.

Bidirectional communication between grafts and host circuits has also been documented. In organotypic and *in vivo* preparations, grafted mouse ventral mesencephalic neurosphere-derived DA neurons engaged in polysynaptic interactions with host neurons. Silencing striatal neurons increased excitatory drive to transplanted cells, while optogenetic stimulation of channel rhodopsin 2-transduced grafted neurons enhanced excitatory currents in neighboring graft neurons, revealing robust intragraft and host-graft connectivity[195].

Furthermore, optogenetics has been employed to directly manipulate grafted neurons, demonstrating their essential role in mediating therapeutic effects. hESC-derived DA neurons engineered to express halorhodopsin could be selectively silenced *in vitro*, suppressing both firing and DA release[196]. After transplantation into parkinsonian mice, these neurons restored motor function and integrated into striatal circuitry. Strikingly, optogenetic silencing of the grafts abolished behavioral recovery, directly indicating that graft activity is indispensable for therapeutic benefit. These experiments highlight that DA-rich grafts not only survive but also modulate host glutamatergic transmission and drive circuit repair.

Collectively, electrophysiological evidence demonstrates that successful transplantation requires more than survival and DA release; it depends on authentic synaptic integration into basal ganglia circuits. Future translation will benefit from *in vivo* patch-clamp methods, multimodal imaging, and closed-loop neuromodulation to rigorously characterize graft-host communication. Establishing standardized electrophysiological endpoints will be essential to define the quality, stability, and clinical relevance of neuronal integration in PD cell therapies.

These studies confirm that grafted neurons can integrate into host networks, prompting the next question: how might this integration influence non-motor symptoms and higher-order brain functions?

### *3.8. Impact of cell therapies on non-motor symptoms and higher-order circuitry*

While cell transplantation consistently improves motor symptoms in PD, many patients and animal models continue to experience non-motor deficits, such as cognitive impairment, mood disturbances, sleep disorders, gastrointestinal dysfunction, and autonomic dysregulation, which often emerge early and significantly impair quality of life[197]. These deficits largely reflect degeneration in extranigral regions, including limbic structures, prefrontal cortex, brainstem nuclei, peripheral autonomic circuits, and the hippocampus, alongside widespread $\alpha$-SYN accumulation that disrupts neurogenesis and contributes to depression[198].

Most cell-based research emphasizes motor recovery, with limited systematic evaluation of cognitive and affective endpoints. Nonetheless, emerging evidence suggests that transplanted DA neurons can integrate into host networks and modulate cortical and subcortical activity, potentially improving emotional, cognitive, and autonomic functions. Preclinical studies confirm that DA modulation extends beyond motor control: mesolimbic DA supports emotional processing, projections to the prelimbic cortex and dorsomedial striatum regulate cognitive flexibility and goal-directed behavior, and dorsolateral striatal circuits contribute to anxiety regulation and decision-making[199-201].

Rodent models with partial or bilateral 6-OHDA lesions recapitulate working memory[202,203] and emotional processing[204] deficits, observed in patients. Some impairments respond to acute (but not chronic) L-DOPA administration, highlighting a narrow therapeutic window[205]. Pharmacological DA restoration improves working memory, response inhibition, and reinforcement learning, correlating with increased prefrontal cortex and caudate activity[206-208]. Clinical trials support the role of DA in affective regulation. For example, pramipexole reduced depressive symptoms independently of motor effects in a 12-week randomized trial[209]. Conversely, apathy frequently emerges after subthalamic nucleus DBS, often linked to DA agonist withdrawal and decreased mesolimbic DA, with preoperative non-motor fluctuations and anxiety predicting susceptibility.

fVM grafts have alleviated cognitive and neuropsychiatric deficits in preclinical models. In 6-OHDA-lesioned rats, striatal reinnervation reduced apathetic-like behavior and restored goal-directed actions[210,211]. DA receptor 2-mediated reductions in cerebral blood volume further implicate DA in pain modulation. Clinical studies corroborate these findings, showing that patients receiving fVM transplants performed similarly to healthy controls on cognitive tests. Improvements in immediate and delayed verbal recall were observed at 12−24 months, although these benefits declined by 36 months[212]. A double-blind trial of 40 patients showed cognitive stability following bilateral fVM transplantation, confirming safety despite limited initial benefit[213].

Early-phase trials of allogeneic iPSC-derived DA progenitors indicate safety, with some subjective non-motor improvements reported (*e.g.*, MDS-UPDRS III, PD questionnaire-39), although effects were inconsistent at 24 months[49]. MSCs may improve non-motor outcomes by differentiating into serotonergic, cholinergic, and noradrenergic phenotypes. Autologous MSC delivery *via* intravenous or intranasal routes produced short-term gains in depression, sleep quality, daytime sleepiness, and overall non-motor symptom scores[214].

A pilot study of unilateral autologous BM-MSC transplantation observed motor improvements accompanied by reduced freezing, enhanced facial expression, and lower medication requirements, suggesting mood and cognitive-motor integration[55]. CB glomus cells may influence non-motor symptoms *via* paracrine modulation of noradrenergic and serotonergic systems essential for mood and autonomic balance[215].

Mechanisms underlying these effects remain incompletely defined. Beyond DA replacement, transplanted cells may act *via* retrograde signaling, glial modulation, and stimulation of endogenous plasticity through local microenvironment enhancement. Grafts may indirectly influence higher-order networks by reshaping host activity or supporting repair in extranigral regions. Emerging tools, including multimodal imaging and single-cell transcriptomics, will be valuable for clarifying how transplanted cells engage limbic and cortical circuits to modulate behavioral outcomes.

In summary, non-motor symptoms constitute a critical but under-addressed component of PD. Evidence indicates that transplanted neurons can influence cognitive, affective, and autonomic domains, particularly when projections reach associative or limbic regions. Successful therapy depends not only on cell survival and DA release but also on the precise reconstruction of functional host-graft circuitry. Future clinical studies should therefore incorporate non-motor endpoints and explore cell types or combinatorial strategies capable of addressing the full pathological spectrum of PD.

Importantly, the potential of cell therapies may be maximized when combined with existing pharmacological and surgical interventions (*e.g.*, levodopa, DBS) or with emerging disease-

modifying approaches such as gene therapy, neurotrophic factor delivery, and biomaterial scaffolds. These synergistic opportunities are discussed in the following Section (3.9).

### *3.9. Synergistic strategies combining cell therapy with established and emerging Parkinson's disease treatments*

The future of PD therapy increasingly emphasizes multimodal approaches that combine cell-based transplantation with established symptomatic treatments and emerging disease-modifying technologies. Rather than standalone interventions, cell therapies are most effective as components within a broader therapeutic ecosystem aimed at enhancing graft viability, accelerating functional recovery, and extending therapeutic durability across PD's heterogeneous and progressive landscape.

Pharmacological support remains essential. L-DOPA, the cornerstone of symptomatic management, can aid motor function and facilitate rehabilitation during the latency period before grafted DA neurons establish robust connectivity and DA release[216]. Dose and duration must be carefully titrated, as excessive stimulation, particularly in the presence of serotonergic contamination within the graft, can induce graft-induced dyskinesias[217]. Personalized regimens, informed by graft maturity, host responsiveness, and dyskinesia profiles, are therefore critical.

DBS, targeting the subthalamic nucleus or globus pallidus interna, provides robust control of motor symptoms in advanced PD[218] and may complement cell therapy through synergistic mechanisms. Next-generation DBS systems with sensing capabilities can detect real-time electrophysiological biomarkers of graft activity, enabling adaptive stimulation. Preclinical models show that closed-loop DBS aligned with pathological oscillations improves outcomes[219], while clinical studies demonstrate that gamma oscillations in the subthalamic nucleus or motor cortex reflect DA tone and symptom severity, guiding adaptive DBS protocols[220]. These approaches illustrate the translational potential of biomarker-driven neuromodulation to support graft integration and long-term efficacy.

Preclinical work underscores that the electrophysiological milieu critically shapes graft outcomes. Building on the integration mechanisms discussed in Section 3.7, hiPSC-derived midbrain DA neurons transplanted into the SN of 6-OHDA-lesioned RAG2-KO mice displayed stable DA-like firing and circuit incorporation[146]. Intranigral graft placement more closely restores physiological nigrostriatal circuitry than intrastriatal delivery, and DBS may help establish a permissive network environment for graft survival and functional integration by normalizing aberrant basal ganglia oscillations.

Gene therapy offers another complementary avenue. Viral vectors encoding DA-synthesizing enzymes (TH, L-amino acid decarboxylase) or neurotrophic factors (cerebral DA neurotrophic factor (CDNF), GDNF, neurturin) can promote axonal sprouting, enhance TH expression, and increase striatal DA tone[221], supporting graft survival, maturation, and integration of transplanted DA neurons.

Bioengineering strategies are increasingly applied to improve graft outcomes. Co-transplantation of DA progenitors with supportive cell types such as MSCs or CB glomus cells within engineered biomaterials (hydrogels, nanofibrous scaffolds) enhances cell retention, nutrient diffusion, axonal growth, synaptogenesis, and local immune modulation[63-65]. Controlled release of bioactive agents mitigates neuroinflammation and reduces dependence on systemic immunosuppression. For example, electroconductive self-healing hydrogels scavenge ROS and rescue ~88% of inflamed neural stem cells *in vitro*, while alleviating neuroinflammation and neurodegeneration in 6-OHDA rat models[222].

These combinatorial approaches not only improve graft viability and circuit reconstruction but also enable patient-specific strategies. Factors such as disease stage, biological age, immune competence, and comorbidities should guide regimen design to align therapeutic intensity with individual risk profiles and optimal treatment windows. Collectively, these strategies mark a shift toward integrative neurorestoration, embedding cell therapy within coordinated pharmacological, neuromodulatory, genetic, and biomaterial-based interventions. Future studies should focus on systematic evaluation of multimodal protocols, supported by longitudinal biomarker tracking and adaptive trial designs tailored to the dynamic needs of PD patients.

While these combinations can optimize graft survival, integration, and function, long-term success ultimately depends on the resilience of transplanted cells within the hostile PD brain. Among the earliest and most pervasive stressors is mitochondrial dysfunction, which compromises both native and grafted neurons. The following section explores mitochondrial biology in PD, detailing how bioenergetic deficits, altered dynamics, and impaired quality control intersect with cell therapy outcomes and represent critical therapeutic targets.

## 4. Mitochondrial dysfunction in Parkinson's disease: A central pathomechanism with therapeutic implications

The selective vulnerability of DA neurons in PD arises from intrinsic features such as extensive axonal arborization, high metabolic demand, limited antioxidant capacity, and disrupted calcium homeostasis[85,223]. Among the many intersecting pathogenic processes, mitochondrial dysfunction emerges as a central contributor, supported by strong evidence from both familial and sporadic PD[224-226]. Mitochondrial abnormalities encompass impaired energy production, altered dynamics and trafficking, and defective quality control mechanisms, including mitophagy. Many of these deficits manifest prior to overt neurodegeneration, implicating mitochondrial dysfunction in both disease onset and progression[227].

Genetic studies further underscore the role of mitochondria in PD pathogenesis. Mutations in PD-associated genes, such as *SNCA*, leucine-rich repeat kinase 2 (*LRRK2*), parkin (*PRKN* ), PTEN-induced kinase 1 (*PINK1*), Parkinson protein 7 (*PARK7*), and the glucocerebrosidase gene (*GBA*) disrupt mitochondrial homeostasis *via* diverse mechanisms[228]. For instance, $\alpha$-SYN exerts mitochondrial toxicity through its oligomeric forms. These oligomers associate with mitochondrial membranes, impair oxidative phosphorylation, reduce ATP production, and trigger cellular stress, ultimately driving neuronal dysfunction and death[229].

Taken together, converging genetic, biochemical, and environmental evidence positions mitochondrial dysfunction at the core of PD pathogenesis, highlighting mitochondria as a critical target for therapeutic intervention.

### *4.1. Bioenergetic failure and complex I deficiency*

A defining biochemical hallmark of PD is the selective impairment of mitochondrial complex I (NADH:ubiquinone oxidoreductase), the first and largest enzyme of the electron transport chain. This deficiency is consistently observed in postmortem brain tissue from PD patients, most prominently in

the SN, but also in extranigral regions such as the frontal cortex and putamen[230-232]. Similar downregulation of complex I has been reported in peripheral tissues, including skeletal muscle, platelets, lymphocytes, and skin fibroblasts[233-235]. These deficits appear independent of aging, disease duration, or neuronal loss, indicating a primary pathogenic role. Notably, they are not associated with mitochondrial DNA mutations, deletions, or copy number changes, pointing instead to post-transcriptional regulatory defects or functional inhibition.

Reduced complex I limits ATP synthesis and disrupts the $NAD^+$/NADH ratio[236], resulting in electron accumulation, enhanced ROS production (particularly superoxide at complexes I and III) and oxidative damage to lipids, proteins, and nucleic acids. This contributes to a self-perpetuating cycle of mitochondrial dysfunction, redox imbalance, and neuronal injury[224]. Additionally, oxidative stress disrupts mitochondrial dynamics and impairs mitophagy, worsening energy deficits and triggering neurodegeneration through apoptotic and necrotic pathways.

Neurotoxin models further support this mechanism. Agents such as MPTP and rotenone, which selectively inhibit complex I, reproduce several PD features, including nigrostriatal DA neuron loss, LB-like inclusions, motor deficits, and glial activation[237,238]. These models remain essential for investigating PD pathomechanisms and evaluating potential therapeutic strategies, underscoring the centrality of complex I dysfunction in PD pathogenesis.

### *4.2. Altered mitochondrial dynamics: fusion and fission imbalance*

Mitochondria maintain cellular and bioenergetic homeostasis through continuous cycles of fusion, fission, and mitophagy, processes that regulate organelle morphology, size, shape, and intracellular distribution, predominantly critical in neurons with polarized architecture and high energy demands. Fusion promotes mitochondrial integrity and content exchange and is regulated by the GTPases mitofusin 1/2 (MFN1/2) on the outer mitochondrial membrane (OMM) and optic atrophy 1 (OPA1) on the inner membrane[239].

Conversely, fission segregates damaged mitochondria and facilitates quality control *via* mitophagy. It is mediated by outer membrane adaptors, including mitochondrial fission factor, fission protein 1 (FIS1), and mitochondrial dynamics proteins 49 and 51, which recruit the cytosolic GTPase dynamin-related protein 1 (DRP1). DRP1 oligomerizes at fission sites to constrict and divide the mitochondrial membrane[240,241]. While fission is essential for organelle distribution and quality control, excessive fragmentation is linked to mitochondrial dysfunction and impaired biogenesis[242]. Fusion and fission are finely regulated by post-translational modifications, including ubiquitination, phosphorylation, acetylation, *S*-nitrosylation, and SUMOylation, allowing mitochondria to adapt to cellular stress[243].

Balanced mitochondrial dynamics are crucial for neuronal function, influencing synaptic development, presynaptic maturation, dendritic spine formation, and synaptic transmission[244]. Dysregulation of these processes has been increasingly implicated in neurodegenerative diseases, including PD. Knockdown of MFN2 in hiPSCs impairs neurogenesis and synaptogenesis[245], while DRP1 ablation in *Drosophila* disrupts mitochondrial trafficking to synapses, causing synaptic dysfunction[246].

Indicators of mitochondrial fusion impairment in the inner membrane, including protein marker alterations and electron-dense deposits, were observed in both sporadic PD SN samples and cellular PD models[247]. Fibroblasts from individuals with biallelic OPA1 mutations displayed extensive mitochondrial fragmentation and disrupted network organization[248]. Likewise, MFN2 deletion in murine models resulted in severe defects in mitochondrial morphology, respiration, and intracellular localization, accompanied by progressive degeneration of the nigrostriatal DA pathway[249,250].

Pharmacological inhibition of DRP1 with dysanore restored mitochondrial homeostasis and activated PINK1/Parkin-mediated mitophagy in MPTP-treated mice, leading to neuroprotection and improved functional outcomes[251]. These findings highlight the therapeutic potential of targeting fusion and fission balance to counteract neurodegeneration in PD.

### *4.3. Impaired mitochondrial axonal transport*

Axonal transport is essential for neuronal homeostasis, enabling bidirectional trafficking of proteins, lipids, organelles, and synaptic vesicles along the axon. This process relies on ATP-driven motor proteins along microtubules. Kinesins mediate anterograde transport toward the axon terminal, whereas cytoplasmic dyneins facilitate retrograde transport back to the soma for recycling and degradation. Kinesins are heterotetrameric complexes composed of two kinesin heavy chains (KHC) and two light chains (KLC), with activity regulated *via* post-translational modifications[252,253]. Dynein function is similarly modulated through phosphorylation of dynein intermediate chains by kinases such as casein kinase[252,254].

Axonal transport involves both fast-moving cargoes, like mitochondria and vesicles, and slower elements, such as cytoskeletal proteins, all vital for neuronal viability and synaptic transmission. Mitochondria are especially critical due to neurons' high energy demands and polarized architecture. Mitochondrial movement is primarily microtubule-based, coordinated by the OMM GTPase Miro and adaptor proteins Milton (Trak1/Trak2). Disruption of Miro or Milton impaired anterograde transport and caused abnormal mitochondrial distribution in *Drosophila* models[137,255]. Miro knockdown also diminished retrograde motility *in vitro*[256]. At presynaptic terminals, mitochondria are anchored by syntaphilin, which interacts with dynein and the neuron-specific kinesin KIF5A[257].

Dysregulation of axonal transport contributes to mitochondrial dysfunction and neurodegeneration in PD. In early-stage idiopathic PD (Hoehn and Yahr stages I−II), decreased KHC and KLC1 levels were observed in SN DA neurons, correlating with disease severity and preceding neuronal loss[258]. Dynein reductions occur predominantly in late-stage PD (Hoehn and Yahr stages IV−V), suggesting a temporal progression of transport impairment, beginning with early anterograde mitochondrial disruption followed by retrograde deficits. Efficient mitochondrial trafficking is therefore critical for neuronal survival, positioning axonal transport dysfunction as an early and progressive pathogenic mechanism in PD.

### *4.4. Defective mitophagy and mitochondrial quality control*

Mitophagy, a selective form of autophagy, maintains mitochondrial quality by targeting damaged or residual mitochondria for lysosomal degradation. This preserves bioenergetic efficiency, limits ROS accumulation, and supports neuronal viability. Dysfunctional mitochondria are typically engulfed by double-membraned autophagosomes, which fuse with lysosomes for

enzymatic degradation. When lysosomal function is compromised, alternative clearance pathways, such as extracellular vesicle release, may compensate[259].

The PINK1/Parkin pathway is the primary regulator of stress-induced mitophagy. Under normal conditions, PINK1 is imported into healthy mitochondria and rapidly degraded. Upon mitochondrial depolarization, full-length PINK1 accumulates on the OMM, phosphorylating ubiquitin and the E3 ubiquitin ligase Parkin, which facilitates Parkin recruitment from the cytosol. Activated Parkin ubiquitinates various OMM proteins, including MFNs and voltage-dependent anion-selective channel 1, marking damaged mitochondria for autophagic clearance[260,261]. Ubiquitin chains are recognized by autophagic adaptors such as p62/SQSTM1, mediating their incorporation into LC3-positive autophagosomes.

Besides mitophagy initiation, the PINK1/Parkin pathway regulates mitochondrial biogenesis and morphology. Parkin-mediated degradation of the transcriptional repressor PARIS (ZNF746) upregulates PGC-1$\alpha$, a master regulator of mitochondrial biogenesis[262]. Parkin also ubiquitinates MFN1 and MFN2, promoting fission through enhanced DRP1 recruitment, facilitating segregation of damaged mitochondrial fragments for degradation[261].

Although extensively studied in stressed immortalized cells, PINK1/Parkin-mediated mitophagy in mature neurons remains less clear. *In vivo* studies in *Drosophila* and mammalian brains report limited Parkin translocation to mitochondria under basal conditions, suggesting reliance on alternative mitophagy pathways[263,264]. In DA neurons, mitophagy likely occurs predominantly in distal axons, which may elude bulk tissue analyses[265]. Deletion of PINK1 or Parkin in mice did not lead to mitochondrial accumulation but instead reduced mitochondrial mass and size[266,267], indicating broader roles in turnover and biosynthesis.

While PINK1 and Parkin mutations account for a small subset of familial PD, growing evidence implicates pathway dysregulation in sporadic PD. Postmortem studies of PD and diffuse LB brains, as well as MPTP models, revealed *S*-nitrosylation and reduced Parkin activity under oxidative stress[268]. Fibroblasts from PINK1 mutation carriers exhibited impaired mitochondrial respiration and membrane potential, recapitulating features of late-onset PD[269]. Similarly, patient-derived iPSC models showed defective Parkin recruitment, increased mitochondrial DNA content, and abnormal mitochondrial biogenesis in DA neurons with PINK1 mutations[270]. Immunohistochemistry also revealed PINK1 colocalization with LBs in 5%−10% of brainstem neurons from heterozygous PINK1 mutation carriers[271], suggesting partial involvement in idiopathic PD.

These findings underscore defective mitophagy and impaired mitochondrial quality control as key contributors to PD pathogenesis. Therapeutic strategies that enhance PINK1/Parkin signaling, restore lysosomal function, or modulate mitochondrial turnover hold promise for disease modification.

### *4.5. Mitochondrial integrity in cell-based replacement therapies*

Emerging regenerative strategies increasingly recognize mitochondrial health as critical for therapeutic success. Cell-based replacement interventions using DA neurons derived from pluripotent stem cells aim to restore the nigrostriatal pathway, but graft survival, integration, and functional maturation depend heavily on maintaining mitochondrial integrity, dynamics, and bioenergetic capacity.

Postmortem analyses of patients up to 14 years after fVM transplantation showed elevated immunoreactivity for Tom20 (an OMM marker) in grafted neurons relative to host cells[272]. This correlated with healthy mitochondrial distribution across neuronal somata and axons, consistent with physiological DA neuron architecture. Similarly, autologous transplantation of hiPSC-derived DA neurons into the putamen of non-human primates revealed morphologically intact mitochondria in both cell bodies and neurites, without fragmentation or pathological clustering[72].

Intercellular mitochondrial transfer further supports graft viability and host neuron survival. Stereotaxic delivery of MSCs enabled transfer of healthy mitochondria to damaged host cells *via* tunneling nanotubes, enhancing mitochondrial function and survival[273]. Furthermore, co-culture studies showed that hiPSC-derived astrocytes transfer mitochondria to DA neurons through a tunneling nanotube-independent, p38 MAPK-dependent mechanism[71]. Astrocyte-derived mitochondria confer resistance to rotenone-induced mitochondrial toxicity, highlighting neuroprotective potential.

These findings highlight mitochondria's dual role in PD, serving as vulnerable targets of pathology and as active mediators of repair in cell-based therapies. Maintaining mitochondrial health, appropriate intracellular distribution, and competence for intercellular transfer in transplanted neurons is essential for effective integration and sustained functional recovery. Interventions aimed at optimizing mitochondrial quality control, such as pharmacological preconditioning, genetic enhancement, or co-transplantation with mitochondrial donor cells, may further enhance graft performance and therapeutic efficacy.

Future investigations should prioritize elucidating the molecular mechanisms governing mitochondrial dynamics, inter-organelle communication, and intercellular mitochondrial transfer within the transplantation environment. A deeper mechanistic understanding will guide the development of next-generation cell therapies that leverage mitochondrial regenerative capacity to more effectively counteract PD.

Because mitochondrial stress and bioenergetic deficits undermine both native and transplanted neuron survival and function, emerging therapeutic paradigms increasingly incorporate supportive strategies to mitigate these vulnerabilities. The following section will examine paracrine and neuroprotective mechanisms, including exosome-mediated signaling, neurotrophic factor delivery, and immune modulation, that promote graft viability and functional integration in the PD brain.

## 5. Molecular and supportive signaling pathways in cell-based regeneration for Parkinson's disease

While the preceding sections have examined the challenges of DA neuron loss and the limitations of conventional replacement approaches, it is increasingly clear that the benefits of cell-based therapies in PD extend beyond simple cell substitution. Transplanted cells can influence disease progression through three complementary mechanisms: release of extracellular vesicles carrying regulatory cargo, secretion of neurotrophic factors that support neuronal survival and plasticity, and modulation of the host neuroimmune environment to enhance graft acceptance and repair (Fig. 6). Together, these processes form a multifaceted regenerative network that underpins the therapeutic potential of next-generation cell-based strategies. The following subsections examine each mechanism in detail.

### 5.1. *Therapeutic potential of exosomes in cell replacement strategies*

Extracellular vesicles, including exosomes, microvesicles, and apoptotic bodies, were secreted by diverse cell types and classified based on size, biogenesis, and molecular composition. Exosomes, the smallest subset (30−150 nm), originated from the endosomal pathway *via* inward budding of multivesicular bodies, which subsequently fused with the plasma membrane to release their cargo extracellularly[274]. They were abundant in body fluids and carried a broad repertoire of bioactive molecules, including proteins, lipids, and various RNA species, reflecting the cell of origin[275].

Exosome biogenesis was primarily orchestrated by the endosomal sorting complex required for transport (ESCRT) machinery: ESCRT-0 clustered ubiquitinated cargo, ESCRT-I and -II drove membrane invagination, and ESCRT-III catalyzed vesicle scission with the assistance of vacuolar protein sorting 4 ATPase[276]. ESCRT-independent mechanisms, such as tetraspanin-enriched microdomains and phosphatidylserine-mediated budding, also contributed. Surface proteins, including tetraspanins (CD9, CD63, CD81), lysosomal-associated membrane proteins, MHC molecules, integrins, annexins, and Rab GTPases, facilitated targeting, trafficking, and interactions with recipient cells[277].

Functionally, exosomes were shown to mediate intercellular communication by delivering regulatory molecules, particularly miRNAs, that modulate gene expression and influence PD pathology[278,279]. Pathological $\alpha$-SYN was detected in cerebrospinal fluid exosomes from individuals with PD and dementia with LBs, implicating vesicles in toxic protein propagation[280,281]. $\alpha$-SYN itself impaired exosome biogenesis by downregulating ESCRT components, exacerbating protein accumulation and spread[282]. Age-related microglial dysfunction further increased the release of $\alpha$-SYN-containing exosomes, whereas inhibiting microglial activation or vesicle secretion suppressed $\alpha$-SYN transmission and neurodegeneration in PD models[280,283].

Several PD-related genes have been reported to intersect with exosomal pathways. Mutations in *ATP13A2* impaired lysosomal function and hindered $\alpha$-SYN degradation, whereas *ATP13A2* overexpression facilitated $\alpha$-SYN clearance through vesicle release[284]. *LRRK2* mutations disrupted autophagy and exosome trafficking, and elevated neuronal exosomal L1 cell adhesion molecule correlated with LRRK2 pathology and may serve as a biomarker[285,286].

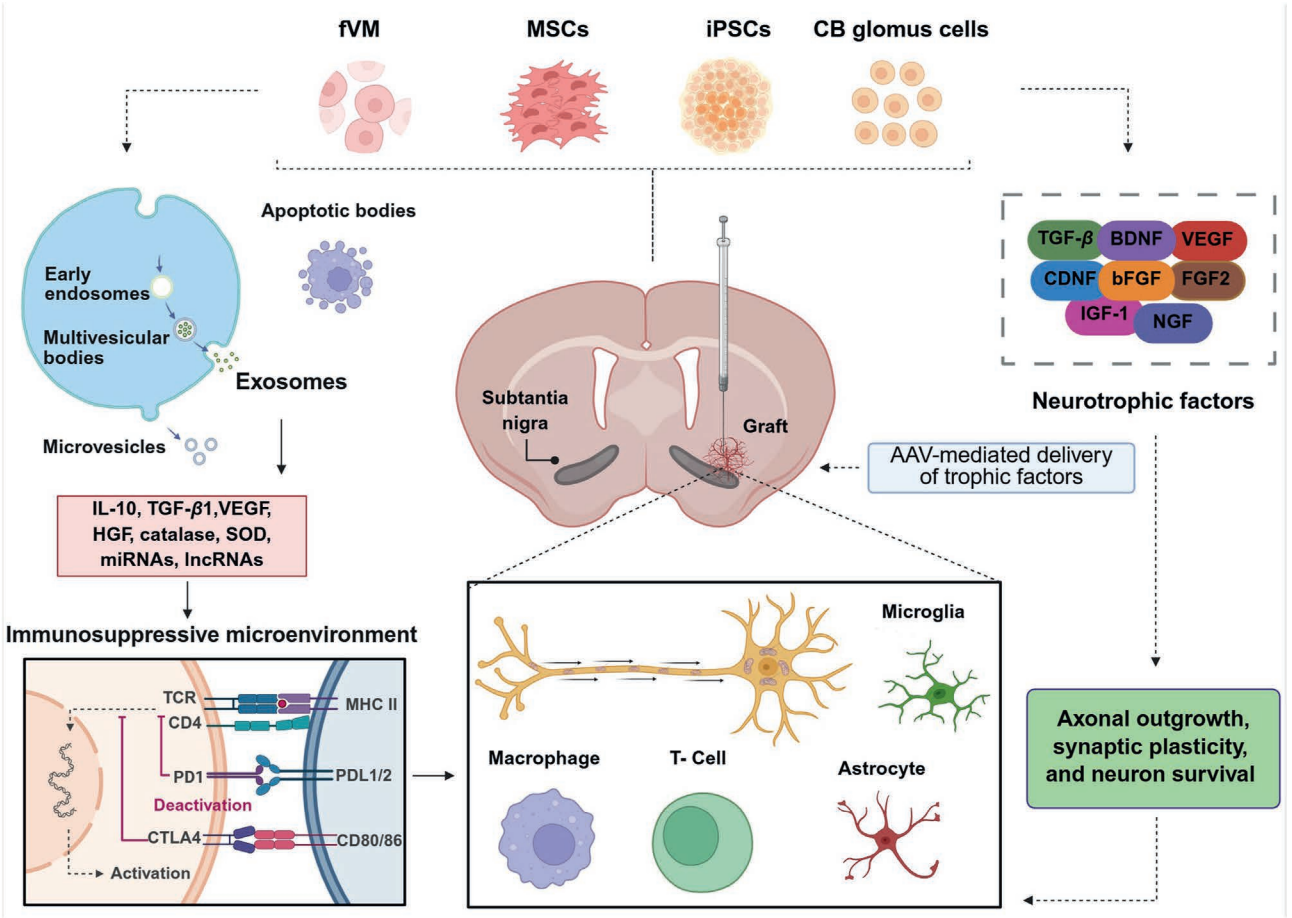


**Figure 6** Therapeutic mechanisms of cell-based regeneration in Parkinson's disease. Transplanted cells promote repair through multiple complementary mechanisms. Extracellular vesicles, including exosomes, microvesicles, and apoptotic bodies, deliver anti-inflammatory cytokines, trophic molecules, and regulatory RNAs that support neuronal survival and help establish an immunosuppressive microenvironment conducive to graft acceptance. Concurrently, neurotrophic factors, either secreted by grafted cells or delivered *via* viral vectors, enhance axonal outgrowth, synaptic plasticity, and dopaminergic neuron survival. Together, these interactions between graft-derived signals and host neural, glial, and immune cells create an integrated regenerative network that underpins the therapeutic potential of cell-based strategies in Parkinson's disease.

Exosomal miRNAs were also shown to modulate PD-relevant pathways. MiR-7, often downregulated in PD, targeted *SNCA* mRNA to inhibit α-SYN expression, attenuating its propagation and neuroinflammation in experimental models[287,288]. MiR-4639-5p, enriched in neuronal exosomes, downregulated *DJ-1*, increasing oxidative stress and DA neuron vulnerability. Its levels were epigenetically regulated by histone deacetylase 11[289,290]. MiR-137 suppressed oxidation resistance 1 (*OXR1*), a key antioxidant gene, and its inhibition (or *OXR1* restoration) mitigated oxidative injury, improved motor function, and enhanced neuronal survival in PD models. Blocking exosomal miR-137 similarly mitigated oxidative damage and rescued pathological features[291].

MSC-derived exosomes are of particular interest because they can cross the blood−brain barrier, have low immunogenicity, and remain stable in circulation[70]. Their cargo includes anti-inflammatory cytokines (interleukin (IL)-10 and TGF-β1), growth factors (vascular endothelial growth factor, VEGF) and hepatocyte growth factor, HGF), neuroprotective enzymes (catalase and superoxide dismutase), and regulatory RNAs (miRNAs and lncRNAs). These components promote neuronal survival, modulate immune responses, protect against complement-mediated cytotoxicity, and enhance angiogenesis, neurogenesis, and axonal outgrowth[70,277].

In PD models, human adipose-derived stem cell exosomes improve apomorphine-induced rotational behavior, preserve SN DA neurons, and reduce microglial activation[69]. Human umbilical cord MSC (hUC-MSC) exosomes restore TH levels, suppress glial activation, and improve motor function in MPTP-injected mice[292]. Dental pulp stem cell- and MSC-derived vesicles protect against DA neuron loss and vascular dysfunction, with BM-MSC secretomes showing similar benefits that are largely attributable to their exosomal fraction[293-295].

hUC-MSC-derived exosomes, which exhibit high proliferative and self-renewal capacity, improve neuron survival and DA content in SH-SY5Y cells and PD animal models[296,297]. These effects are partly mediated by the transfer of neuroprotective miRNAs such as miR-100a-5p, miR-133b, and miR-188-3p[298-300]. Therapeutic strategies using miRNA mimics (miR-124, miR-7) or antagomiRs (miR-155, miR-126) further modulate inflammasome activity, reduce α-SYN aggregation, and exert anti-inflammatory and neuroprotective effects[301]. Despite these promising preclinical findings, exosome-based diagnostics and therapies remain in early clinical development.

### *5.2. Neurotrophic factor signaling in cell-based regenerative medicine*

Beyond vesicle-mediated communication, transplanted cells secrete neurotrophic factors such as BDNF, CDNF, GDNF, insulin-like growth factor 1, FGF2, nerve growth factor, TGF-β, and VEGF[172,174]. These molecules support axonal growth, synaptic remodeling, neuronal survival, and immunomodulation by suppressing microglial activation and promoting tissue repair.

Poor graft survival in trophic-deficient or immune-reactive environments remain a major obstacle[302]. Strategies to enhance neurotrophic factor signaling include pretreating donor cells with neurotrophins, co-transplanting cells engineered to secrete neurotrophic factors, and delivering exogenous factors *via* viral vectors, encapsulation devices, or hydrogels[303-305]. For instance, combining GDNF with fVM grafts improves DA neuron survival and integration in rodents and primates, while encapsulated GDNF-producing cells protect both host and graft[65,306]. Similarly, CDNF- or GDNF-releasing microcarriers promote graft maturation and axonal extension in hemiparkinsonian rats[307].

hiPSC-derived grafts highlight the importance of trophic support. Patient-derived fibroblasts and iPSCs exhibited dysregulated neurotrophic factor and receptor expression during DA differentiation[308]. Co-transplantation of hiPSC-derived PITX3-eGFP$^+$ fVM progenitors with adeno-associated viral vector-mediated GDNF delivery into the SN or striatum improved graft integration, restored DA levels, and enhanced behavioral outcomes in 6-OHDA rats, with effects correlating to GDNF distribution[309]. In MPTP-lesioned primates, adeno-associated viral vector encoding GDNF promoted axonal extension from human fetal neural stem cells toward the striatum, although most cells failed to mature into DA neurons, indicating that regional cues were also required[310].

MSCs naturally provide robust trophic support and could be engineered for enhanced output. hUC-MSCs overexpressing VEGF, FGF2, or BDNF increased neuronal differentiation, reduced glial activation, and improved neuroprotection in PD models[311-313]. Similarly, BM-MSCs engineered to produce BDNF or CDNF preserved DA markers and recovered motor function in 6-OHDA rats[314,315]. Preconditioning BM-MSCs with basic FGF or modifying them to co-express GDNF and TH further increased DA levels, enhanced motor outcomes, and protected against MPTP-induced damage in monkeys[316,317].

CB-derived cells, which secreted high levels of GDNF, provide paracrine neuroprotection without directly replacing DA neurons. CB transplantation stimulated endogenous nigrostriatal regeneration, promoted axonal sprouting, and yielded sustained clinical improvements in PD patients[183,318].

### *5.3. Neuroimmunomodulatory considerations in cell-based approaches for Parkinson's disease*

The central nervous system immune landscape plays a pivotal role in graft survival and integration. Allogeneic grafts, including unmatched fVM tissue or iPSC-derived neurons, usually require systemic immunosuppression to prevent rejection[302,319,320]. However, long-term immunosuppressive regimens carry significant risks, and even autologous or HLA-matched iPSC-derived neurons can trigger immune responses due to mitochondrial or epigenetic incompatibilities[68,321-324]. Immune-engineered iPSCs with HLA deletion or checkpoint ligand overexpression (programmed death-ligand 1, CD47) were developed to evade immune surveillance and prolong graft survival[325,326].

Certain donor cell types, mainly MSCs and CB-derived cells, exert intrinsic immunoregulatory effects by secreting IL-10, TGF-β, neurotrophic factors, and extracellular vesicles that suppress microglial activation, reprogram macrophages, and recruit regulatory T cells, mechanisms that indirectly support DA neuron regeneration[189,190,327]. CB-derived glomus cells additionally release pro-inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor α), which influence neuronal excitability and host-graft interactions[327].

MSC-related immunomodulation could be further amplified through preconditioning or genetic modification. FGF2 reduced chemokine CCL11 in dental pulp-derived MSCs *via* c-Jun N-terminal kinase signaling[328]. Hypoxia-preconditioned human olfactory mucosa MSCs secreted TGF-β1, enhancing DA mitochondrial function through microglial ALK/PI3K/Akt signaling, with Phase I trials confirming the safety of intraspinal transplantation in PD[329]. Preconditioning MSCs with α-SYN promoted stemness, glycolysis, and autophagy-related miRNA profiles,

activating lysosomal/autophagic pathways that increased DA neuron survival and potentially countered $\alpha$-SYN toxicity[61].

To limit systemic immunosuppression, localized strategies have been developed, such as microparticle-based sustained-release tacrolimus (FK506), immunomodulatory hydrogels, and semi-permeable encapsulation devices that create restricted immune privilege[66,330]. These approaches are particularly relevant in PD, where chronic systemic immunosuppression is undesirable.

In summary, effective regenerative strategies need to couple neuronal replacement with precise immune modulation. Future approaches are likely to combine immune-shielding biomaterials, co-transplantation of immunoregulatory cells, and bioactive scaffolds to optimize graft survival, integration, and functional recovery.

## 6. Conclusions and future perspectives

Despite significant advances in symptomatic management, PD remains incurable. This highlights the urgent need for regenerative strategies that go beyond simple DA replacement. Long-lasting L-DOPA therapy is often complicated by motor fluctuations and dyskinesias. DBS and ablative procedures provide symptomatic relief but remain palliative, as they do not alter the underlying neurodegenerative process. These limitations emphasize the critical need for disease-modifying interventions.

Cell-based approaches have emerged as a promising avenue, encompassing fVM transplantation, iPSC-derived grafts, supportive MSCs, and CB glomus cells. These procedures show potential to reconstruct DA circuits, restore striatal innervation, and provide neuroprotective effects. Nevertheless, clinical translation faces significant challenges, including immunological rejection, heterogeneity in graft composition, and uncertainties about long-term functional integration and safety.

Future research should focus on promoting graft survival and function by combining cellular engineering, immune modulation, and biomaterial-based precision delivery. Incorporating disease-relevant markers such as synaptic pathology, mitochondrial dysfunction, and neuroinflammation may improve patient stratification and prognostic accuracy. Additionally, standardized protocols and robust regulatory frameworks will be essential to ensure safety, reproducibility, and scalability.

By integrating advances in molecular neuroscience, regenerative medicine, and neurotechnologies such as neuroimaging and electrophysiology, next-generation treatments could shift the paradigm from symptomatic management to true neuroprotection and circuit-level repair. If these challenges are successfully addressed, cell-based regenerative interventions have the potential to transform the therapeutic landscape of PD, offering durable, disease-modifying benefits and improved long-term quality of life for patients.

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## Author contributions

Victor Tapias designed and conceptualized the article. Ana Lizeth Padilla and Victor Tapias wrote the initial manuscript, prepared the tables, and contributed to revisions. Ana Lizeth Padilla, José L. Lanciego, and Victor Tapias prepared the figures. José L. Lanciego, Miquel Vila, Fernando de Castro, Fernando Rodríguez de Fonseca, Antonia Serrano, David Pozo, Javier Sáez-Valero, Lucía Núñez and Carlos Villalobos participated in the discussion and revision of the manuscript. All authors have read and agreed to the published version of the article.

## Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

AI-assisted tools were employed exclusively to enhance the clarity and overall quality of the writing. All content was reviewed and edited by the authors, who take full responsibility. No scientific content was generated by AI; the manuscript reflects the authors' original work.

## Conflicts of interest

The authors declare no conflicts of interest.

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